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Original Communications

FRACTURE OF THE FEMORAL NECK FOLLOWING ROENTGEN THERAPY FOR GYNECOLOGIC MALIGNANCY

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OCCURRENCE of fracture of the neck of the femur as a sequel to radiation therapy for gynecologic malignancy is a serious complication. Excluding pathologic fracture due to metastases, the evidence is becoming more conclusive that some fractures may be directly attributed to the radiation effects on the normal bone and its vascular supply. Indeed when we consider that in irradiating pelvic malignancies the bony structures must necessarily be exposed, it is surprising that more complications are not noted. In some techniques, notably when true lateral trochanteric portals are used to attack the neoplasm, the femoral necks and their blood vessels receive an unusually large amount of direct radiation in addition to backscatter from other portals. More emphasis must be placed on the possibility of fracture as a sequel to such exposure.

Adult bone has always been considered as relatively resistant to radiation. This is a relative statement which should not be interpreted as meaning that adult bone is wholly immune to such effects. If enough radiation is given, the vascular, periosteal and bone changes will inevitably be such as to result in serious complications.

The literature confirmed our own findings of fracture of the femoral neck as a complication of irradiation for pelvic malignancies. However, this appeared for the first time in American literature in 1936.[1]

It is our intention to review all the reported cases, to discuss the pathogenesis, and to emphasize further the conclusive nature of the evidence by presenting cases of our own.

In the treatment of advanced cancer, we must realize the true limitations and be content with palliation rather than intensive therapy, the consequences of which might be worse than the original disease. Only the tyro will rush up with radiologic heavy artillery in a last-minute attempt to save a patient already doomed by advanced malignancy. But, since early cancer, if neglected, inevitably leads to death, only prompt and radical therapy may avert a fatal outcome. Even here,

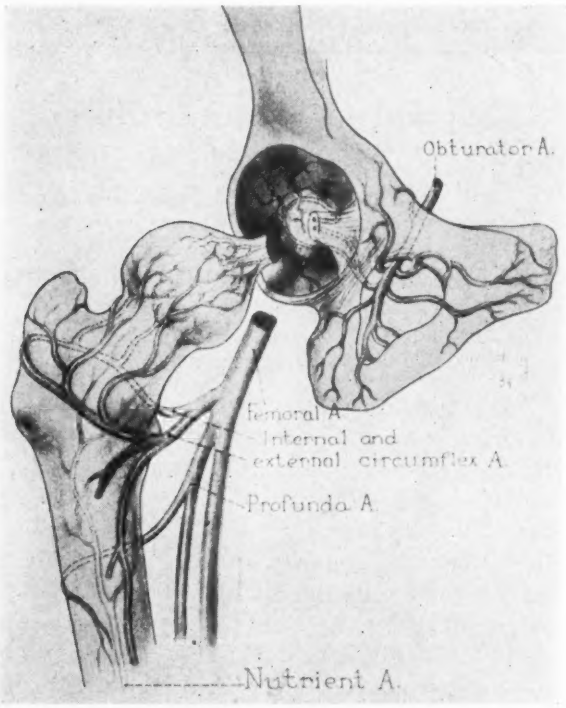

Fig. 1.—Schematic illustration of the blood supply of the head and neck of the femur.

however, enthusiastically intensive therapy may lead to sequelae which are often serious and occasionally calamitous and certainly fracture of the femoral neck is one of these. Since the use of lateral ports increases the incidence of fracture, we must ask whether the so-achieved slight increment in depth dose justifies their use.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

As noted by Kolodny,[2] the subject of femoral neck fractures is still obscure even to orthopedists; to gynecologists it is almost alien. Indeed, only since the advent of high voltage therapy has the subject assumed any gynecologic significance. The blood supply to the femoral neck, comparatively poor at best, is derived from the vessels of the periosteum, diaphysis, and ligamentum teres. With advancing age, the last named diminishes in importance.

The anatomy of these parts can best be described by quoting Gray:[3] "The acetabular branch (of the medial femoral circumflex artery) arises opposite the acetabular notch and enters the hip joint beneath the transverse ligament in company with an articular branch from the obturator artery; it supplies the fat in the bottom of the acetabulum, and is continued along the round ligament to the head of the femur." Elsewhere, Gray[4] says: "The nutrient artery of the femur is usually given off from the second perforating artery; when two nutrient arteries exist, they usually spring from the first and third perforating vessels." He[5] further states: "The anterior surface of the neck (of the femur) is perforated by numerous vascular foramina." Spalteholz[6] also demonstrated vascular foramina along the linea intertrochanterica.

Lippman and Zemansky[7] have shown that, in animals, the vessels of the round ligament are essential for the normal development of the femoral head until maturity and that interference with the circulation results in deformity. After

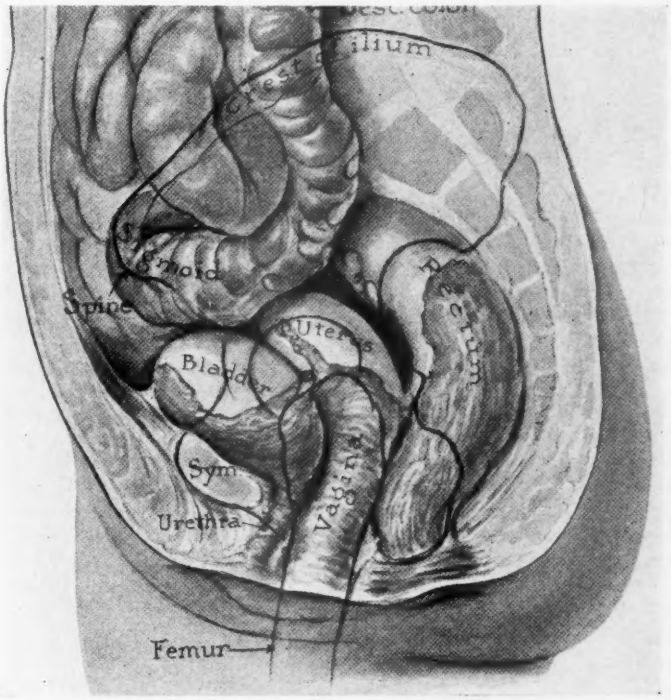

Fig. 2.—Femoral outline superimposed over pelvic viscera. (Permission of S. H. Camp Co.)

adolescence when the epiphysis has united with the shaft the importance of these vessels diminishes, they no longer carry blood into the femur and nutrition of the head is derived entirely from below. They assume that the same changes occur in the human being. The round ligament arteries are functionally end arteries and though capillary anastomoses between them and the peripheral epiphyseal branches do occur; experiments have shown that they are insufficient to preserve the viability of the affected part. Lippman,[8] in another study in which he quotes Bergman, mentions the significance of the occlusion of the lateral epiphyseal vessels in producing pathologic changes. Since Albee[9] finds that it is necessary to conduct blood to the anemic capital fragment in his treatment of femoral fractures, may we not infer that vascular disturbances may be an etiologic factor?

Kolodny[10] states that the nutrition of the femoral head and neck in advanced middle life depends upon the diaphyseal end branches, the periosteal blood vessels,

and especially the epiphyseal vessels and very little upon those vessels in the ligamentum teres. He concludes his study as follows: "The question of healing of fractures of neck is entirely dominated by the difference of nutritional conditions in different types of fractures and in various ages of the patient." The present paper is, of course, concerned only with adult bone. A personal communication from A. F. Sava, based on a number of anatomic dissections, states: "The circulation of the femur proximal to the intertrochanteric line is supplied via capsular vessels . . . circumflex branches of the femoral. These form a complete ring about the femur (at the intertrochanteric line) and from this vascular ring branches run upward to supply the surgical neck and the head of the femur. I see no way in which these very important vessels could escape being in the line of fire in deep therapy of the pelvic structures, particularly through a lateral port."

NONRADIATION CAUSES OF SPONTANEOUS FRACTURE

Nutritional Defects.—Another factor which concerns the study of fractures is nutrition. Impaired diet resulting in basic nutritional deficiencies such as demineralization due to the disturbed calcium-phosphorus-vitamin D relationship has long been known in pediatrics. The study of adult nutrition unfortunately has not kept pace with that of the child. A recent editorial[11] has stressed the importance of gradual demineralization, affecting not only the skeleton, but the kidneys and other vital organs as well. Maxwell[12] has shown that acute calcium-vitamin D starvation in the adult is the etiologic factor in osteoporosis. The generalized form of osteoporosis may be a gradual and asymptomatic form of osteomalacia. Bernheim[13] has demonstrated that, with senescence, the ability of the intestinal tract to absorb mineral salts decreases. Other investigators have linked the gradual decrease of hydrochloric acid content in gastric secretions of older persons with diminished calcium absorption, resulting in possible osteoporosis. With the exception of the parathyroid and the ovary, the relationship of the other endocrines to this disturbance is not sufficiently established. Recent experimenters are administering estrogens in the treatment of fractures.

Metastases.—The most frequent cause of spontaneous fracture seen by the oncologist is that due to metastases. However, in 1900 (before radiation therapy could affect the statistics), Cullen[14] stated: "The patient usually dies before there has been sufficient time for extension to the bones to take place. Some cases, however, have been observed." Bone metastasis from cervix carcinoma is of such rarity that it is the subject of a forthcoming paper.

Taylor[15] and others have emphasized the value of radiation castration in mammary cancer. This is predicated on the basis of a hormonal relationship. If a castration dose (in breast cancer) is sufficient to combat or prevent bone metastases, should not a relatively much larger dose given for a pelvic malignancy be even more efficacious in inhibiting bone metastases? May this not be the reason why bone metastasis from cervical malignancy is so rare when treated radiologically?

RADIATION THERAPY

The etiology, prophylaxis, and treatment of bone injury have become even more complicated with the advent of higher roentgen dosages by the single massive or the prolonged continuous techniques. Until recently adult bone had been considered relatively immune to radiation. As late as 1928, Groedel and Lossen[16-18] in their encyclopedic volumes on *Roentgen Accidents and Injuries, etc.*, fail to mention spontaneous fractures of the femoral neck as a possibility. This we regard as highly significant. In 1930, Flaskamp in his monograph, *Damages Through X-rays and Radioactive Substances*[19] says, "The healthy bone of the adult appears to be very radio-resistant." Even in 1934, Colwell and Russ[20] say: "Adult bone is relatively resistant to x-ray and injuries from this cause are rare. . . . We are unaware of any bone lesions reported from this cause." They further state that out of hundreds of cases of mammary cancer irradiated they had never seen injury to bone or cartilage. However, in a recent personal communication, Pack mentioned five cases of rib fracture following radiation therapy for mammary cancer. Colwell and Russ, nevertheless, do remind us that the unprotected hands and wrists of the pioneers did develop undue fragility and de-

creased bone density. They attributed this to vascular changes impairing bone nutrition, which were prominent in such cases.

On the other hand, as far back as 1922, Regaud[21] noted bone necrosis following x-ray or gamma radiation. He thought that the calcium and phosphorus of the bone set up secondary radiations of a more caustic nature which caused damage to the vital parts of the osseous tissue. This action may remain latent until some determining cause stirs it into activity, e.g., trauma or microbial infection. Even earlier, in 1910, Cluzet[22] had demonstrated that radiation inhibits or delays the formation of callus after fractures; this is probably due to the devitalized osteoblasts in the periosteum which prevent bone regeneration. Recamier[23] demonstrated experimentally that bone growth could be retarded by a roentgen dose so small that it effected no change in the skin or histologically demonstrable changes in the bone cells. Ewing[24] states that the periosteum of all bony structures is most susceptible to irradiation. Regaud[25] says: "The irradiated bone burns and burns the periosteum and mucosa enveloping it."

The subject of osteoradionecrosis is thoroughly covered by Watson and Scarborough,[26] who attribute its development to irradiation, trauma, and then infection. Roentgenograms are of little value in the early stages of this disease. Late osteoradionecrosis has been observed by them eight and one-half years after successful treatment. According to them, "Syphilis is definitely not a factor in the etiology." They warn us: "It has been recognized that the responsibility for the serious complication of osteoradionecrosis rests entirely with the physician who outlines and carries out the irradiation measures, just as the surgeon must assume the major responsibility for an operative death."

SURVEY OF CASES REPORTED

The literature shows Baensch[27] to be the first to have reported a case of osseous injury following gynecologic irradiation. However, in his report in 1927 he credits Perthes and Jungling with having previously reported bone necrosis in connection with a roentgen ulcer. He also mentions Rahm observing mandible necrosis without preceding ulcer. In 1932 Baensch[28] reported a second case and concluded, "Without doubt the spontaneous fractures described above were attributed to the effect of irradiation because no other condition responsible for a pathologic fracture could be found."

Philipp,[29, 30] in 1932, reported four cases of postradiation fracture in which no skin breakdown occurred. He states that he had never seen a spontaneous fracture unless the patients had received therapy from lateral ports. All of his patients received large but not excessively large doses. He concluded: "In forensic respects these cases are of importance in so far as one cannot infer an overdosage from the development of a fracture."

Kropp,[31] in 1934, also reported a case. Baclesse[32] and Regaud have observed three cases. We quote a personal communication: "We have observed three cases of such a fracture. In two cases there was evidently no metastasis because patients were living more than five years after x-ray application. In the third case, the radiographical findings were not so evident; the patient, treated four years ago, is still alive and suffering from her fracture, which is not actually healed. Is there a metastasis? We are following the patient." It is very likely that radiation therapy might have modified the osseous structures of the femoral neck to such an extent that "however insignificant a trauma might have produced a fracture."

The first American cases of this condition were reported by Dalby, Jacox, and Miller[1] in 1936. They cited 14 histologically demonstrated pelvic malignancies. In no instance was neoplastic growth demonstrated roentgenographically at the fracture site.

The radium was given via tandem tubes in the uterus and a bomb application against the cervix for an average dose of 5,000 to 6,000 mg. hr. They emphasize that "radium, as generally employed, probably has little effect on the femoral neck." Furthermore three of their patients received no radium at all. The x-ray therapy factors were 200 KVP, 0.5 mm. Cu. through four portals of 10 by 15 cm. in size, applied over two anterior and two posterior oblique fields. No lateral

TABLE I. SUMMARY OF REPORTED CASES OF FRACTURE OF NECK OF FEMUR FOLLOWING RADIATION

AUTHOR	AGE OF PT.	CARCINOMA OF	RADIUM MG. HR. OR MC. HR.	NO. OF CASES	ROENTGEN THERAPY DOSAGE PER PORT	PORTALS		A	P	INTERVAL BETWEEN THERAPY AND FRACTURE	FRACTURE ONE OR BOTH	COMMENT
						2 LATERAL	OBLIQUE					
Baensch, 1927	45	Cervix	7244	1	2 sed	+		+	+	3 yr.	Both	
Baensch, 1932	62	Ovary	None	1	?	+		+	+	1½ yr.	Right	Autopsy
Phillip, 1932	62	Cervix	Moderate dose	1	Large dose	+		+	+	Soon	Both	
Phillip, 1932	68	Cervix	6864	1	2 sed	+		+	+	2 yr. 2 yr. 2 mos.	Right Left	
Phillip, 1932	55	Cervix	None	1	2 sed	+		+	+	2 yr.	Right	Schauta operation before
Phillip, 1932	68	Cervix	5088	1	Over 2½ sed	+		+	+	1 yr.	Left	
Kropp, 1934	67	Cervix	1836 to vault	1	?	0	1 vulva port	+	++	3¼ yr.	Left	Wertheim operation before
Baclesse and Regaud*				3	?							
Dalby, Jacox, Miller, 1936	42	Cervix	5000-6000	14 cases 3 of whom received no radium	1500-2000 r.	0	2 posterior oblique	+ +		19 mo.	3 Bilateral	17,280 r. total 1 autopsy 1 open operation 11,840 r. total
Dalby, Jacox, Miller, 1936	Average age 57 yr.		Tandem and Bomb		Series repeated 2-3 times at intervals of 3-6 months					3 yr. average	11 Unilateral	
Dalby, Jacox, Miller, 1936	78									73 mo.		

Miller and Folsome, 1938				21 cases additional	Same technique		2 posterior oblique	+ +				
Healy and Frazell, 1937	57	Cervix stump	3009 MCH	1	750 r. repeated			+ +	+ +	4½ yr.	Right	
Healy and Frazell, 1937	56	Cervix	3000 MCH	1	1800 r. 1500 r.	+		+ +	+ +	2¼ yr.	Left	
Kalayjian*	68	Cervix	3000	1	1500 r.	0		+ +	+ +	9 months	Both	
Costolow				1								1 case in over 1200 cervix cancers
Henry Schmitz*				1								1 case in over 1000 cervix cancers
Zoe A. Johnston*				2								
Robert G. Douglas*				2								
Clara Okrainetz		Ovary		1		Rt. +						

*Personal communication.

trochanteric ports were used. Each series consisted of approximately 200 r. (measured in air) applied to each port every second to fourth day until a total of 1,500 to 2,000 r. was reached. The series were repeated two or three times at intervals of three to six months. In 6 patients the skin over the treated area was found in perfect condition. Two showed considerable telangiectasia, 6 showed bronzing and none showed serious skin damage or ulceration. An average period of three years (shortest 19 months, longest 73 months) intervened between the diagnosis of malignancy and fracture. The fractures were bilateral in 3 cases, occurring at intervals of ten, thirteen, and fourteen months, respectively. In no case was there a history of trauma. However, every patient complained of pain starting in the hip and radiating down the anterior thigh to the knee, for an average of seven months before the fracture was demonstrated. Pain on motion or weight bearing was also noted. However, the typical radiating pain described above may be due to ureteral stenosis.[33]

There were only two histologic studies of the fractured structures, one a result of an open operation and the other an autopsy following death from an injury. In addition to radium, these patients received 17,280 r. and 11,840 r., respectively.

"The incidence of fracture of the femoral neck in this series is definitely higher than in a comparable group of the general population."[34] "An incidence of 2.1 per cent appears to be more than incidental."

In 1938, Miller and Folsome[35] mention 21 additional proved cases of spontaneous hip fractures in their clinic since the report in 1936. This brings their total number up to 35 cases.

Healy and Frazell,[36] in 1937, reported two such cases in over 3,000 pelvic malignancies irradiated.

Kalayjian,[37] in 1938, reported a case of bilateral fracture of the femoral neck.

In the course of discussion at the American Radium Society Meeting at San Francisco, June, 1938,[38] the following additional cases were reported: Costolow of the University of Southern California, 1 case (over 1,200 carcinomas of the uterus treated); Henry Schmitz of Chicago, 1 case (in over 1,000 cervical carcinomas treated); Zoe A. Johnston of Pittsburgh, 1 case.

In a subsequent personal communication, Dr. Z. A. Johnston mentioned that she had seen another case.

Robert G. Douglas of the New York Hospital has seen two cases. Clara Okrainetz[39] of Montefiore Hospital, New York City, reported a case in 1939.

In order to determine if there were other nonreported cases, a questionnaire was sent out. Those reporting in the affirmative (published and unpublished) have been detailed above. To show the rarity of this condition, note that the following have not observed any cases:

B. F. Schreiner, State Institute for Malignant Diseases, Buffalo
Edw. F. Skinner, St. Luke's, St. Mary's, Kansas City General
A. E. Hayward Pinch, London Radium Institute
Curtis F. Burnam, Howard Kelly Hospital, Baltimore
Francis C. Wood, Crocker Institute & St. Luke's Hospital, New York City
Lawrence A. Pomeroy, Cleveland City and Lakeside Hospital
A. N. Arneson, Washington Univ. Med. School, St. Louis, Mo.
U. V. Portmann, Cleveland Clinic
Geo. E. Pfahler, University of Pennsylvania, Philadelphia
Geo. G. Ward, Woman's Hospital, New York City
A. U. Desjardins, Mayo Clinic
Charles L. Martin, Baylor University
Maurice Lenz, Columbia-Presbyterian, N. Y., Med. Center
Charles A. Walters, Johns Hopkins Hospital
Rollin H. Stevens, Grace Hospital, Detroit
H. B. Hunt, Univ. Neb., Neb. M. E. Hospital, Douglas Co. Hospital
H. H. James, Murray Hospital, Butte, Mont.
James Heyman, Radium Hemmet, Stockholm

Dr. U. V. Portmann made the following comment: "It is quite likely that the bone changes are produced by irradiation of lateral fields to the pelvis, which I

never use.'' Dr. Chas. L. Martin wrote: ''Never used lateral ports and our technics have never been of the excessively severe type.'' May not the absence of cases in the above clinics be due to the technique and dosage?

PERSONAL OBSERVATIONS

CASE 1.—Mrs. L. S., a 37-year-old Jewess, was admitted to the Brooklyn Cancer Institute Jan. 5, 1938, with the complaint of profuse postcoital bleeding of ten days' duration.

Family and Past History irrelevant except menopause at the age of 26, when both ovaries were removed because of some obscure post-partum complication.

Present Illness.—Five months ago she noticed a scant whitish, watery, nonblood-tinged leucorrhea. Ten days before admission, following coitus, she noted profuse vaginal bleeding which has persisted.

Admission examination was negative except for the vaginal examination which showed a mobile cervix, high in vaginal vault with no parametrial infiltration or thickening. The anterior lip was smooth and regular. The posterior lip had a small proliferative nodular growth, no larger than the ''tip of the finger,'' which bled on manipulation. Corpus and adnexa were negative. Rectal examination confirmed the vaginal. Impression: ''If this is a carcinoma of the cervix, it is a Schmitz No. 1 and amenable to treatment.''

Laboratory reports were entirely negative except the *biopsy* which showed transitional cell carcinoma of the cervix.

Complete pelvic cycle of roentgen therapy was given between January 11 and April 1, 1938 (38 treatment days), using the following factors: 6 ports to the pelvis, 10 by 15 cm. each, 2 anterior, 2 lateral, 2 posterior, rotating right and left side daily; 200 r. units to each port for a total of 3,000 r. units measured in air, without backscattering; 200 kv.; 20 Ma., 2 mm. Cu., 1 mm. Al., filtration; 50 cm. S.T.D. She received 15 treatments to each port, cross-firing the pelvis as indicated. For each 100 r. given at skin without backscattering the different depths received doses shown in Table II.

TABLE II

DEPTH	100 R. AT SURFACE WITHOUT BACKSCATTER	3000 R. TOTAL PER PORT	
0 cm.	136 r.	4080 r.	
1 cm.	140 r.	4200 r.	
2	133	3990	
3	120	3600	
4	109	3270	
5	98	2940	
6	88	2640	
7	78	2340	
8	69	2070	
9	61	1830	
10	54	1620	
11	48	1440	
12	42	1260	Tumor dose
13	38	1140	calculated as
14	34	1020	being the sum
15	31	930	of the depth
16	28	840	doses given
17	25	750	through each
18	22	660	port.

Tumor dose is approximately 7,620 r. units. The tumor dose, without lateral ports, would have been 5,940 r. units. For each 100 r. units at the surface each anterior port contributed 51 r., the posterior 48 r. and the lateral 28 r.

One week after completing therapy, patient was admitted to hospital for insertion of radium. Vaginal examination showed cervix to be smooth, firm, flush with the

vaginal vault, freely movable and no parametrial infiltration. X-rays at this time showed no evidence of pulmonary or osseous metastases. Phenolsulphonephthalein test normal. Pyeloureterogram negative.

Under cyclopropane anesthesia, 6 radium needles were inserted into the cervix and a colpostat into the fornices. Factors: Six 2 mg. radium element needles, 35 mm. long, ½ mm. Pt. filter = 12 mg. Two 20 mg. radium element tubes in a colpostat, 1.0 mm. Pt. filter = 40 mg.; duration, 74 hours; dosage, 3,848 mg. hr.

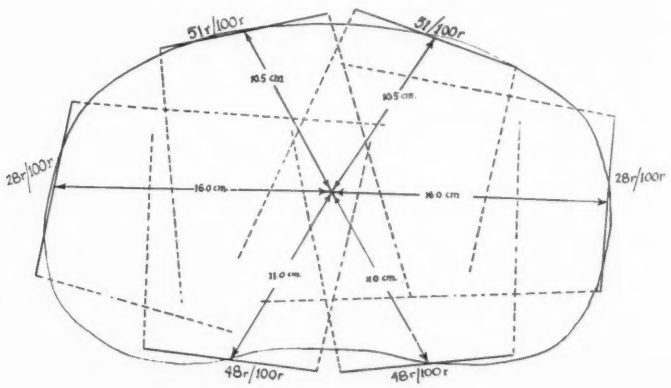

Fig. 3.—Case 1. X-ray therapy factors and dosage.

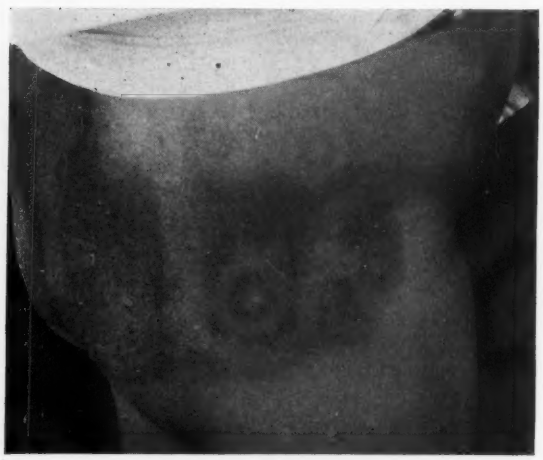

Fig. 4.—Case 1. Radiation reaction outlining right lateral port.

Two weeks later a uterine tandem was introduced after dilatation of the cervical canal. Factors: A tandem of three 10 mg. tubes of radium element (30 mg.), 1 mm. of Pt. filter; duration, 50 hours; dosage, 1,500 mg. hr.

Five months after starting roentgen therapy she first complained of pain in right thigh radiating down to the knee.

Three months later she complained of pain in upper portion of right thigh and in an area lateral to the sciatic notch. Flexion of the hip with the knee extended yielded pain in above areas, also when walking upstairs or attempting to rise from a chair. No other pain was complained of.

X-rays of the pelvis and upper three-fourths of the right femur were negative.

Six weeks later (ten months after initial visit) rectal examination revealed indurated tissue encircling anterior half of the rectum about six inches from anus. Proctoscopy distal to the stenotic area showed many pin-point areas of hemorrhage on the anterior and right rectal wall. Biopsy from this area was nonmalignant.

On Oct. 20, 1938, a barium enema was given and reported as follows: "The barium enema flows in without difficulty until it reaches a point eight inches above the anus. Here, a slight delay takes place and the lumen of the sigmoid for a stretch of one inch is narrowed to one-half inch diameter and the outline is irregular. After evacuation the mucosal pattern in the constricted area was preserved.

Fig. 5.—Case 1. Fracture of right femoral neck. Stricture of large intestine. Barium enema after evacuation.

There is an intracapsular fracture of the right femur. The fracture line runs at right angles to the axis of the neck and is very straight. There is upward displacement of the distal fragment by about one-half inch. The bone does not show any visible pathologic changes. Conclusions: Organic constriction within the distal half of the sigmoid. Fracture of right femoral neck." The fracture was thus noted six months after completion of therapy and four months after onset of pain in the hip.

Blood chemistry, count, and sedimentation rate were normal. Wassermann and Kline tests were negative.

Blood calcium was 9.08 mg./100 c.c.; phosphorus, 4.63 mg./100 c.c.; phosphatase, 7.61 units.

A body spica plaster cast extending from the umbilicus down to the right ankle and to the left knee was applied.

Within a month of the application of the cast, the patient developed bronchopneumonia and severe pain beneath the cast, necessitating its removal. Extensive

radiation changes in the skin over the radiated ports were noted. X-rays at this time "did not show bony callus." Sandbags were used for immobilization.

Jan. 10, 1939, one year after the initial visit, a careful check-up showed that her phenolsulphonephthalein test was now 31 per cent in two hours and a marked bilateral hydronephrosis and hydroureter had developed. A rectovaginal fistula was found. Vesicovaginal fistula was suspected, but never proved because of her general condition. She developed pain in her left hip which gradually became more severe; repeated roentgenograms failed to show osseous changes which might precede a fracture. Clinically and roentgenographically she showed signs of intestinal obstruction. She died Jan. 29, 1939, one year and twenty-four days after her initial visit.

Autopsy report by Dr. Herman Bolker, Pathologist. The following are the essential findings on post-mortem study. Several loops of ileum were bound in the pelvis and intimately adherent to one another. They were kinked upon themselves at several points, and in one loop there was an irregular, punched out, ulcerated area with a necrotic base roughly 2 cm. in diameter, which extended in the gross into the muscularis; no evidence of it was seen on the serosal surface. From a point 6 cm. proximal to the anal orifice, the rectal wall was surrounded by a very dense, fibrous tissue, which extended upward for a distance of 10 cm. The muscularis was well defined in this area, but the mucosal folds were flattened, and a large fistula to the vagina measuring 2.5 cm. in diameter was found at a distance of 8 cm. from the anus. The edges were smooth and rolled. There were two other fistulas, both in the anterior wall, one 2 cm. below, and the other 3 cm. above the large fistula. Each of these was 1 cm. in diameter. The only recognizable portion of uterus which remained was a small mass of firm tissue, found in the expected anatomic position of the organ. The urinary bladder was contracted, and thick-walled. Its wall was grayish green in appearance, and resembled that of the vagina, which was also gangrenous. There was considerable periureteral dense fibrous tissue in the parametrial areas. The ureters were not grossly dilated; they could be traced without difficulty to the renal pelves. The calyces and pelvis on the left were slightly dilated.

There were several rectangular brown discolorations of the skin over the upper femoral, sacral, and inguinal regions, bilaterally corresponding to the ports used in the radiation therapy.

The upper third of the right femur was removed, and a distinct coxa vara was noted. On section there was evidence of a healed fracture at the neck corresponding with the roughened area at the inferior edge of the neck externally. The cortex in this area appeared thickened, while the remainder of the cortex about the head was rather thin. The marrow of the head and trochanteric region was yellowish and showed no areas of neoplastic involvement. It was somewhat more dense in the line across the neck. The marrow of the shaft was soft and yellowish red.

The other pertinent findings were vesicovaginal and rectovaginal fistulas, marked parametrial fibrosis and several punched out ulcers in the small intestine, judged due to radiation.

The immediate cause of death was pneumonia.

Microscopic findings were as follows:

Uterus.—The greatest portion of the lining was replaced by a necrotic and purulent layer. Much of the wall had undergone complete coagulation necrosis. Several areas, however, were invaded by sheets of atypical squamous cells, which occurred in discreet groups, and showed central necrosis, lysis, or keratinization. The individual cells had poorly defined cell boundaries, a deep pink cytoplasm, and vesicular or hyperchromatic nuclei, which varied considerably in size and shape. Intercellular bridges were not demonstrable. There were no mitotic figures. Tumor cells were found in the parametrial fatty tissue. There was an infiltrate of moderate numbers of lymphocytes and plasma cells. Many of the large arteries showed considerable subintimal thickening.

Rectovaginal Fistula.—The tract was a necrotic and purulent one. The underlying tissue contained numerous masses of neoplastic cells similar to those found in the parametriums. The vaginal mucosa had undergone coagulation necrosis. There was a scattered mono- and polymorphonuclear leucocytic infiltrate. Recent

thrombi were present in the larger veins. The rectal mucosa showed considerable degenerative change. The mucosal and submucosal blood vessels were widely dilated. The pararectal tissue was a broad mass of fibrous tissue infiltrated with polymorphonuclear leucocytes.

Urinary Bladder.—The lining epithelium had desquamated. The mucosa was markedly edematous. There was considerable vascular dilatation. No neoplastic involvement was found in the vesical or ureteral walls.

Fig. 6.—Case 1. Section (autopsy) through fracture site in femoral neck with fibrosis avascularity.

Fig. 7.—Case 1. Ligamentum teres with vascular lumen markedly narrowed.

Small Intestinal Ulcer.—The mucosa was completely necrotic, being recognized only by small suggestive plicae. The submucous fibrous tissue was greatly increased in amount and had replaced the muscularis in part. The ulcer at one point reached and involved the longitudinal layer of the muscularis. The fibrous tissue was infiltrated with moderate numbers of plasma cells, lymphocytes, and polymorphonuclears. The serosa was also markedly widened and had increased fibrous tissue.

Femur.—In sections through the fracture site, the cortex was absent over a wide area, being replaced by poorly cellular fibrous tissue. This contained numerous

dilated thin-walled vascular spaces. The adjacent cortex was undergoing resorption. Union between the fragments was entirely fibrous. The remaining trabeculae were small and undergoing decalcification. There was no evidence of new bone formation. The adjacent marrow was fatty; small areas of hematopoiesis were present. No neoplastic elements were found. The periosteum was thickened, particularly at the fracture site, and consisted of dense, poorly cellular, fibrous tissue. No osteoblasts were present. Many of the smaller arteries within the marrow and in the periosteal tissues had markedly thickened walls, with almost occluded lumina. The thickening was due almost entirely to widening of the subintimal layer. Inflammatory cellular infiltrate was scant and of the mononuclear variety. Sections through the head of the femur showed a covering of histologically normal hyaline cartilage. The cortex, marrow, and bony trabeculae showed no histologic changes. Sections through the ligamentum teres were composed of considerable dense, fibrous tissue. Several of the smaller arteries in the ligament showed marked subintimal thickening with the lumina narrowed to varying degrees, some being almost completely occluded. Vessels of the same size in the viscera showed no comparable thickening. The sections from the irradiated skin presented an atrophy of the epidermis with flattening of the rete pegs. The underlying corium shows considerable homogenation, and contains numerous chromatophores. There is a scant lymphocytic infiltrate, chiefly perivascular in location.

Fig. 8.—Case 2. Femoral heads moderately deformed, angulated upward. On the upper aspect of the right femoral neck, the cortex shows slight interruption of continuity. Intravenous pyelogram, cystogram, and ureterogram.

Case 2.—Mrs. A. P., a 58-year-old Puerto Rican, para iii, was admitted Aug. 14, 1937, complaining of leucorrhea, weight loss, pelvic pain, and vaginal bleeding of 2 months' duration. Family and past history were irrelevant. Physical findings were mitral stenosis, secondary anemia, and a Schmitz III carcinoma of the cervix uteri. Vaginal examination revealed a firm, nodular, and fixed cervix with an ulcerated crater on its posterior lip, which on biopsy proved to be a squamous cell carcinoma. Parametria were bilaterally infiltrated. Uterus was slightly enlarged; adnexa, negative. Laboratory findings were essentially negative. Phenolsulphonephthalein excretion was low, in spite of negative cystoscopy and pyelography (retrograde and intravenous).

Roentgen therapy given from Aug. 17 to Sept. 25, 1937, consisted of the following factors:

200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration
Six ports (2 anterior, 2 posterior, and 2 lateral), 10 by 15 cm.
200 r. to each of 3 areas daily, rotating right and left, totaling 2,400 r. per port (or 14,400 r.), yielding a tumor dose of 6,814 r. units.

Sept. 27, 1937: Examination after completion of x-ray cycle showed marked regression in local lesion. Cervix was atrophied and flush with vaginal vault, and of normal consistency. Fornices were obliterated. Body of the uterus was atrophic. Parametrial thickening had practically disappeared.

Comment: "Excellent recession of local lesion, but constriction of vault and obliteration of fornices will definitely interfere with proper full radium dosage."

Radium therapy on Sept. 27, 1937, consisted of:

Uterine tandem of 10 and 10 mg.
Vaginal corks of 10 and 10 mg. } 1.5 mm. Pt. filtration
40 mg. × 100 hours = 4,000 mg. hr.

On Sept. 19, 1939, patient returned to the clinic, after an absence of two years, complaining of inability to abduct her thighs. Her weight was 95¾ pounds. "Vaginal examination revealed an obliterated vagina which admitted one finger for a depth of 1½ inches. Cervix, uterus, and adnexa were palpable."

Intravenous pyelography showed both kidneys functioning well.

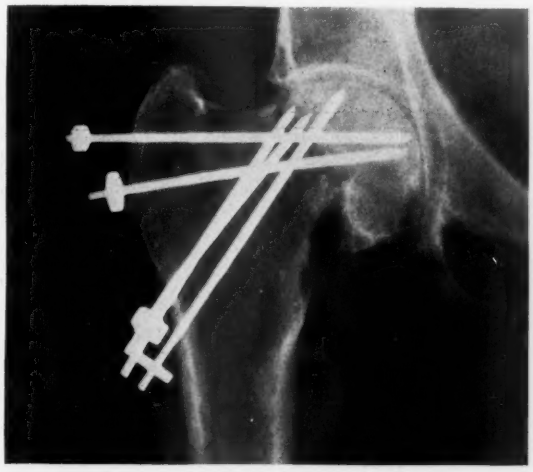

Fig. 9.—Case 3. Intracapsular fracture at junction of right femoral head and neck.

Roentgenographic report: "Bilaterally, the femoral head shows coarse trabeculation and a cherry-sized area of increased illumination surrounded by a ring-shaped shadow of increased density. The femoral head is moderately deformed (angulated upward). On the upper aspect of the right femoral neck, the cortex shows slight interruption of continuity. On the whole, the affection of both femoral heads is very symmetrical."

It was felt that the bone changes noted adequately explained her clinical symptoms. She has repeatedly refused to return to the hospital or even see the social worker.

CASE 3.—Mrs. A. D, a 64-year-old American housewife, para iv, was admitted Aug. 5, 1938, complaining of vaginal bleeding of three months' duration. Her family, past, and marital history were noncontributory, except for a fall five years earlier. Following this fall she promptly arose and walked home. She saw no physician, had no x-ray taken and suffered no disability except slight pain in right thigh with change in weather. Physical examination was irrelevant except for pelvic findings. Vaginal examination: vagina was moderately contracted; cervix, softened, small, smooth and not ulcerated, but there was a slight sanguineous ooze from the external os. Fundus was not enlarged. Bilateral parametrial thickening was present, more marked on the right.

Blood count was normal, serology negative for syphilis. Curettage of cervical canal showed a transitional cell carcinoma.

Radium was inserted on Aug. 10, 1938:

Uterine tandem 15 – 15 – 10 mg. radium
Vaginal colpostat 15 – 15 mg. radium
70 mg. for 92 hours = Dose 6,500 mg. hr.
} 1½ mm. platinum filtration

Roentgen therapy was given between Oct. 17, 1938, and Jan. 6, 1939, and consisted of the following factors:

200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration
Six ports (2 anterior, 2 posterior, and 2 lateral) 10 × 15 cm. in size
200 r. to each of 3 areas daily—alternating left and right for a total of 2,400 r. each measured in air (total 14,400 r.), yielding a tumor dose of approximately 6,204 r.

Fig. 10.—Case 4. Fracture of left femoral neck.

Following this, she gained weight, felt better, and had no complaints until six months later when she complained of pain in her chest. At this time x-ray of chest showed a small area in the right lung which was questionably metastatic.

Five months later, on Dec. 4, 1939, she complained of pain in the right upper thigh. Vaginal examination showed a frozen pelvis with infiltration to the lateral pelvic walls. X-rays of skull, spine, upper extremities, and legs were negative. X-rays of the femora and pelvis showed: "Intracapsular fracture of the right femoral neck with partial impaction and rarefaction in upper half. Sclerosis in the lower half of the fracture line." This was eleven months after completion of therapy. Blood count was normal at this time; blood calcium 9.52 mg. per cent, phosphorus 3.8 mg. per cent, phosphatase 8 units. A lateral splint was applied to immobilize the right femur. Subsequently at open operation, five Moore pins were inserted through the neck to the head of the femur. Healing was prompt. She is walking around with difficulty at present, and her general condition is only fair.

CASE 4.—Mrs. M. F., a 64-year-old Italian housewife, para xii, was admitted May 23, 1938. Cervical biopsy at another hospital showed squamous cell carcinoma, prickle-cell type. Menopause occurred at age of 41 years. For the past year she had a gradually increasing leucorrhea, and for the past month lower abdominal pain and swelling of the left leg. There was no bleeding.

Physical examination was essentially negative, except for pelvic examination which showed a slightly enlarged nodular fixed cervix with bilateral parametrial infiltration more marked on the right. X-ray films of the chest, spine, pelvis, and intravenous pyelography were negative, as were the electrocardiograms, blood count, chemistry, and Wassermann test.

Roentgen therapy consisting of the following factors was given between May 24, 1938, and July 1, 1938:

> 200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration
> Six ports (2 anterior, 2 posterior, and 2 lateral) 10 × 15 cm.
> 200 r. to each of 3 areas daily, rotating right and left totaling 2,400 r. per port (or 14,400), yielding a tumor dose of 5,496 r. units.

Fig. 11.—Case 4. Fracture of left femoral neck, cone study.

Radium therapy was given on July 11, 1938. The factors were:

Uterine tandem 15 and 15 mg.
Vaginal corks 15 and 15 mg.
60 mg. × 100 hr. = 6,000 mg. hr. } 1.5 mm. Pt. filtration

Pelvic examination at this time showed a markedly narrowed vagina, a cervix not palpable, and bilateral parametrial infiltration. The following month she developed a phlebitis of the left lower extremity which subsided under symptomatic therapy.

On April 1, 1940, she walked into the clinic with a noticeable limp and complained of pain in the left hip. This pain had been gradual in onset for the past four months. X-ray showed "intracapsular fracture through the upper end of the left femoral neck with ½ inch upward displacement—and slight impaction of the fragments. No changes of bone structure can be detected."

She had less than 1 cm. shortening, with no appreciable eversion, and slight spasm on inversion. Pelvic findings were: occluded vagina and frozen pelvis. Treatment consisted of immobilization by sandbags, followed by a Thomas splint or walking caliper. She now walks with considerable difficulty.

TABLE III. SUMMARY OF AUTHORS' CASES

Factors used: Dosage calculated for portals in r. units (in air)
6 portals—2 anterior, 2 posterior, and *2 lateral*, 10 × 15 cm.
200 kv., 20 Ma.
Filtration 2 mm. Cu. + 1 mm. Al.
T.S.D. 50 cm.

PATIENTS	FIRST L. S.	SECOND A. P.	THIRD A. D.	FOURTH M. F.
Age	35 yr.	58 yr.	64 yr.	64 yr.
Diagnosis	Cervix carcinoma	Cervix carcinoma	Cervix carcinoma	Cervix carcinoma
Schmitz Class	I	III or IV	III	III
Radium dose mg.hr.	5,348 mg.hr.	4,000 mg.hr.	6,500 mg.hr.	6,000 mg.hr.
Total r. units per port	3,000 r.	2,400 r.	2,400 r.	2,400 r.
Grand total	18,000 r.	14,400 r.	14,400 r.	14,400 r.
Tumor dose	7,620 r.	6,814 r.	6,204 r.	5,496 r.
Tumor dose without lateral ports	5,940 r.	5,206 r.	4,644 r.	4,224 r.
Interval between completion of therapy and diagnosis of fracture	6 mo. rt. femur	24 mo. bilateral	11 mo. rt. femur	20 mo. left femur
Treatment or operation	Body spica and sandbag immobilization	Refused	Operation, 5 Moore pins	Thomas splint or walking caliper
Progress	Autopsy	Barely able to walk	Walking with difficulty	Walking with difficulty

SUMMARY

We feel justified in presenting these cases as fractures of the femoral neck following radiation therapy of cervix carcinoma.

Repeated x-rays, particularly at the sites of fracture, were negative for metastases.

Frequent roentgenograms disclosed no osteitis fibrosa, destructive, neuropathic, or other recognizable bone disease entities.

It is generally conceded that syphilis is not an etiologic factor in this condition.

The incidence of femoral neck fracture in cases of gynecologic carcinoma treated by roentgen therapy is higher than that observed in a similar age group of the population.

Senescence certainly could not be an important factor in the first patient who was only 38 years old at the time of death.

Obesity can be ruled out etiologically, since the patients at most weighed between 96 and 140 pounds during the period of treatment.

Severe trauma is entirely excluded because the first patient was bedridden except for the necessary examinations and the others gave no such history. At no time did they complain of sudden sharp pain. The fracture was insidious and diagnosed fortuitously in the first case during a barium colon roentgenogram. Only one and one-half months previously the femur and pelvis were roentgenographically negative. In the other cases the diagnosis was made because of our previous experience.

Absence of bilaterality does not mitigate against the pathogenesis previously ascribed. If these patients live long enough, it is not improbable that more bilateral fractures will be observed. Our first case died within a year of the completion of her x-ray cycle. The remaining patients are still alive.

Careful histologic examination of multiple sections from the fracture site and adjacent bone revealed no metastatic involvement.

In the case autopsied, since the right lateral trochanteric port received 3,000 r. units and the depth dose to the tumor through this port was 840 r. calculated at 16 cm. depth, the intervening tissue was of necessity irradiated. The skin showed marked bronzing and epithelial desquamation. Subcutaneous induration, ureteral occlusion, intestinal obstruction with stenosis and multiple fistulas were also present. All of these changes were bilateral. Due to the proximity of the femur to the surface, the depth dose to the bone and its vascular supply is practically the same as the surface dose. This must be borne in mind in evaluating the term "relative radiation resistance." Excessive dosage of roentgen therapy whether given in one prolonged cycle or in smaller repeated cycles imperceptibly reaches dangerous proportions whose consequences become more serious with the lapse of time.

The pathologic findings of the autopsy are characteristic of radiation effects.

CONCLUSIONS

This study was undertaken not with the intention of finding fault with the technique of the oncologic radiologist, but with the hope that we may profit, to the benefit of the patients, from a critical survey of the reported data of osseous radiation injury.

It is our conclusion that the small increase of depth dose via treatment through lateral ports does not justify the added risk. Also that doses of radiation even in prolonged, small, divided dosages, by their cumulative action, may produce serious injury even to a radiation-resistant structure-like bone. In repeating the cycle, the cumulative action must be carefully borne in mind.

Clarification of the pathogenesis is a necessary prerequisite for early correct diagnosis. Earlier diagnosis assumes greater importance as the incidence of the condition increases, which is to be expected as the percentage of ten-year survivals following roentgen therapy rises.

We must bear in mind that the vascular supply of the femoral neck is terminal and vulnerable to postradiation vascular occlusion. In most cases these patients are poorly nourished due to a calcium-phosphorus-vitamin imbalance. A critical evaluation of our own work requires us to revise our technique in the light of the above conclusions.

We cannot condemn all therapy which does not cure, since therapeutic nihilism, in a disease fraught with such dire consequences, is craven surrender. If we can do naught but alleviate the symptoms of advanced malignancy and make oncoming death more bearable, we are justified in using palliative therapy. However, we must keep in mind that we are treating the patient and not the disease.

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PREVENTION OF ASPHYXIA NEONATORUM*

A Study of the Etiologic Factors Observed in 2,000 Consecutive Deliveries

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PREVENTION of asphyxia neonatorum should be the acknowledged responsibility of every obstetrician as an integral part of prenatal care and the conduct of labor. There has been a tendency to accept asphyxia neonatorum as something unpreventable or at least unavoidable. Fatalistic acceptance of the latter view might seem justified upon superficial consideration of the fact that prematurity, trauma, and analgesics are ordinarily accepted as most important etiologic factors and that beyond a certain point these are truly unavoidable. This acceptance is confirmed in current literature concerning asphyxia neonatorum where the great majority of publications are concerned with treatment only.

The approach to this problem of prophylaxis should be similar to that of prevention of any disease as conducted along lines of preventive medicine in general. Before prevention can be instituted, a thorough

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knowledge of the incidence, distribution, severity, and other modifying factors of the disease must be obtained. Some work has been done along these lines, and this report adds corroborative evidence, but more will be necessary before the various ramifications of this problem are completely understood.

Until recently, neonatal death has been considered the only serious consequence of asphyxia neonatorum. There can be no doubt about the high neonatal mortality following asphyxia, a fact repeatedly observed and reported.

The entire subject of fetal and neonatal death has been recently summarized by Potter and Adair.[1] Important developments in the field of asphyxia by Yant and associates,[2] Courville,[3] Schreiber,[4] and others have revealed many unfortunate results from asphyxia other than death. The knowledge of the fact that permanent damage to the central nervous system can be caused by anoxia is leading to a revision of our concepts concerning the seriousness of asphyxia neonatorum in those infants who survive. Schreiber's[4] statistics show that 70 per cent of a group of 500 individuals with evidence of neurologic disease of obstetric origin had asphyxia at birth. DeLee[5] has long stressed the importance of observing these individuals in later life.

With the improvement in medical records and statistics, we should be able eventually to observe the asphyxiated infant and its ultimate fate. From the few figures available, the incidence of asphyxia is usually from three to five times greater than that of neonatal death. This makes the group under consideration much larger than the neonatal death group alone and probably embraces between 15 and 25 per cent of all infants.

At the inception of this study, little could be found in the literature concerning statistical evaluation of the many etiologic factors of asphyxia neonatorum. Since then Cole, Kimball and Daniels[6] have analyzed 5,000 consecutive deliveries on the basis of the etiologic factors of asphyxia. Prior to this report most of the literature was concerned with the evaluation of various analgesics and their merits as demonstrated by relationship to the incidence of asphyxia neonatorum. A tabulation of the literature concerning pain relief in labor listed over 400 such articles by 1930; hundreds more have appeared since then. Thus, a critical review of the literature is all but impossible, yet from these reports, the consensus is to date that no one has found a pain-relieving drug which does not reflect itself by increasing asphyxia neonatorum. History indicates that many drugs have been in favor for a short or longer period of time as ideal analgesics, only to fall into ill repute by the test of time. The case of "twilight sleep" is a notable one. In general, there has been too much emphasis placed on the type of drug used and too little knowledge employed in the correct use of any chosen one. The pivotal point has been aptly stated by Clifford and Irving[7] who state that no method of obstetrical analgesia . . . "is without some unfavorable influence on the fetus . . . and the ultimate fate of the present methods of analgesia may hinge on the price the infant must pay for the mother's comfort."

Various fundamental but somewhat isolated facts concerning the etiology of asphyxia neonatorum have appeared in the literature, most of them appearing in conjunction with discussions of pain relief.

The importance of excessive variations in fetal heart rate in relation to asphyxia was emphasized by von Winckel[8] in 1893 and by others since that time. Knipe[9] in his review of "twilight sleep" states that both Hocheisen and he found increased asphyxia following an increase in length of labor. Veit in 2,550 vertex labors reported 18.2 per cent asphyxia following two-hour second stage of labor and 49.6 per cent following a four-hour second stage. Shute and Davis[10] more recently have described in detail the relation of morphine to the condition of the infant at birth. In addition to the effect of morphine itself, which caused 26 per cent narcosis, they found important such factors as time of administration, trauma of delivery, maternal toxemia, condition of the infant in utero, anesthesia and adjuvant sedatives. Lewis[11] concluded that a combination of any of several analgesic agents plus operative delivery greatly increased the incidence of asphyxia. Clifford and Irving[7] observed less asphyxia with barbiturates than with opiates, and that the size of the dose and the time of administration of barbiturates was of no great significance. These later reports were the results of series of selected cases. The relation of trauma and prematurity were reviewed and summarized by Hess, Mohr, and Bartelme[12] who emphasized the relation of cyanosis to atelectasis and cerebral trauma. Clifford[13] reported the relation of asphyxia to premature separation of the placenta.

Kosmak,[14] in 1931, in discussing the viewpoint the obstetrician should take in asphyxia neonatorum, stated that it was something to be feared constantly and anticipated. He divided the causative factors as follows: (1) before delivery: pressure, prolapse and knots of the cord, placental separation, uterine tetany, narcosis, analgesia, and anesthesia. (2) During labor: trauma of forceps, pressure, and version. (3) During labor and delivery from sudden compression or release of the head passing through the birth canal. (4) Prematurity: with defective respiratory development. (5) Asphyxia from analgesics given the mother.

A similar classification by Moncrieff[15] is as follows:

A. Central Factors
   1. Immaturity of the center.
   2. Damage of center: pressure, edema, hemorrhage, etc.
   3. Narcotics.
   4. Chemical factors: oxygen lack, carbon dioxide excess, etc.
   5. Circulatory disturbances: cord pressure, etc.

B. Peripheral
   1. Obstruction.
   2. Delayed expansion.
   3. Muscular feebleness.
   4. Circulatory failure.

McGrath and Kuder[16] studied 4,865 consecutive births in relation to asphyxia neonatorum, their primary interest being the peripheral factors involved. Mention was made that prophylaxis played an important part in reducing the effects of the central factors. They found that trauma increased asphyxia from 6.6 to 15.6 per cent and fetal mortality from 2.4 per cent to 10 per cent.

There has been considerable discussion in the literature about the correctness of the term "asphyxia neonatorum" and various substitutes have been suggested: apnea neonatorum, anarchapnea, respiratory failure, oligopnea, and others. While granting that the term "asphyxia neonatorum" is a misnomer, we feel certain that everyone knows the connotations that the words carry, and hence it will be used.

The opinions, experience, and individual reactions of the obstetrician result in diverse conceptions, first as to what constitutes asphyxia neonatorum, and second, as to the need for resuscitative methods. The perfectly normal newborn infant takes its first breath as delivery is completed or immediately afterwards. This usually occurs within ten or twenty seconds after birth and certainly should occur within a minute. After this, the respiratory passages contain enough air to permit the characteristic loud, vigorous, and lusty cry. Any infant that fails to do this is not physiologically normal at birth, and therefore should be classified as asphyxiated. These infants with abnormal respiratory function manifest one or more of the readily observed signs in Table I.

This classification was the basis for the present study. Occasionally some difficulty was encountered in the classification of mild asphyxia due to incomplete data. This has led to the practice now employed at every delivery; namely, the accurate recording, in seconds, of the length of time from birth until the first breath and also until the characteristic vigorous lusty cry. Both of these are readily observed and constitute end points for judgment of the degree of asphyxia. The actual timing of the institution and duration of resuscitation is also important.

TABLE I. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE* ASPHYXIA
Respiratory	Onset Respiration	Spontaneous Immediate	Spontaneous Oligopnea 1-5 min.	Delayed Apnea 5-15 min.	Delayed Apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous Lusty	Delayed Vigorous Lusty	Delayed Weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous Active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

*All infants alive at onset of labor but who died during labor are included in this group.

In the following clinical-statistical study of over 2,000 consecutive deliveries, we shall attempt to tabulate and evaluate the frequency, severity, and combined effects of some of the etiologic factors that alter the normal respiratory function of the infant at birth. All of the patients were delivered on the obstetric floor of this hospital; they were both private and ward patients, but every case was under the direct supervision of attending staff or trained residents. This fact lends accuracy and uniformity to the data. The results were compiled by a careful study of the completed obstetric record, infant record, and anesthetic record, and then transferred to punch cards. From these cards practically unlimited statistical analyses were possible. Both advantages

and disadvantages were found with the use of completed records; difficulty was encountered occasionally when there was incomplete data. This was offset by the data being entirely impersonal and unbiased. Twenty cases were not used because of lack of data or because the pregnancy was of less than twenty-eight weeks' duration. There was some question as to the proper classification of stillbirths. Inasmuch as many stillbirths are due to asphyxia in labor, only infants dead at the onset of labor (absent fetal heart tones) were excluded. There were 24 of these, 18 of which were found to be macerated at birth.

RESULTS

On the basis of the previously mentioned classification, the following results were obtained from a study of 1,982 infants: No asphyxia, 85 per cent (1,684 cases); mild asphyxia, 6.8 per cent (134 cases); moderate asphyxia, 6.0 per cent (120 cases); severe asphyxia, 2.2 per cent (44 cases). Those classified as no asphyxia had normal respiratory function at birth. The "mild" group were those

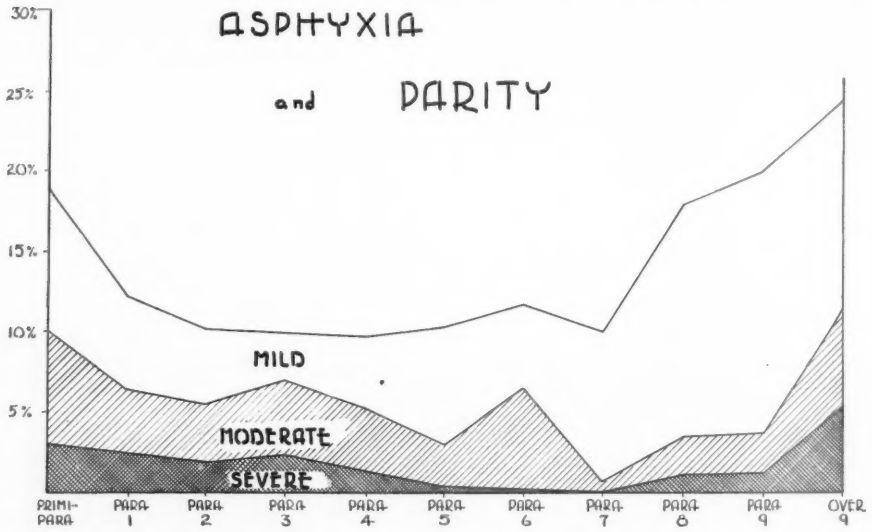


Fig. 1.—The incidence of mild, moderate, and severe asphyxia neonatorum in 890 primiparas and 1,092 multiparas.

apparently not seriously involved and would be considered by many observers as normal infants. To a certain extent the "moderate" group roughly corresponds to the old classification of asphyxia livida. The "severe group contains those previously known as asphyxia pallida but may also contain those with asphyxia and cyanosis.

Parity.—As was expected, the primiparas have nearly twice the incidence of asphyxia that multiparas have, primiparas 18.9 per cent and multiparas 11.7 per cent. Unexpected were the results found in a comparison of the various degrees of parity. The optimum parity occurred with the fourth or fifth child, this was followed by an increase beginning with the eighth pregnancy (Fig. 1). This apparently coincides with the increase in age noted by Cole and others.[6]

Prenatal Complications.—This was one of the important factors noted in this series. An unusually high percentage of complicated obstetric cases are treated at this hospital. Out of 1,684 deliveries, 595, or 30 per cent, had some prenatal complications. The total percentage of asphyxia was over twice as great in these in-

dividuals, being 26 per cent while the uncomplicated cases had only 11 per cent asphyxia. There is a wide variation in the frequency of asphyxia, depending on the type of complication present. In classifying individuals having more than one prenatal complication, the most significant one was chosen. For example, toxemia would receive preference over the common cold. These results are graphically recorded in Fig. 2.

Maturity.—Most reports considering maturity are usually based on the weight of the newborn infant as the criterion of maturity, or on a combination of weight and gestational age. Inasmuch as accurate determination of weight before birth is impossible and even the estimation of weight is subject to gross inaccuracies, we have classified maturity on the basis of gestational age alone. In a survey primarily intended to permit the evaluation of the unborn infant, this seems to be a

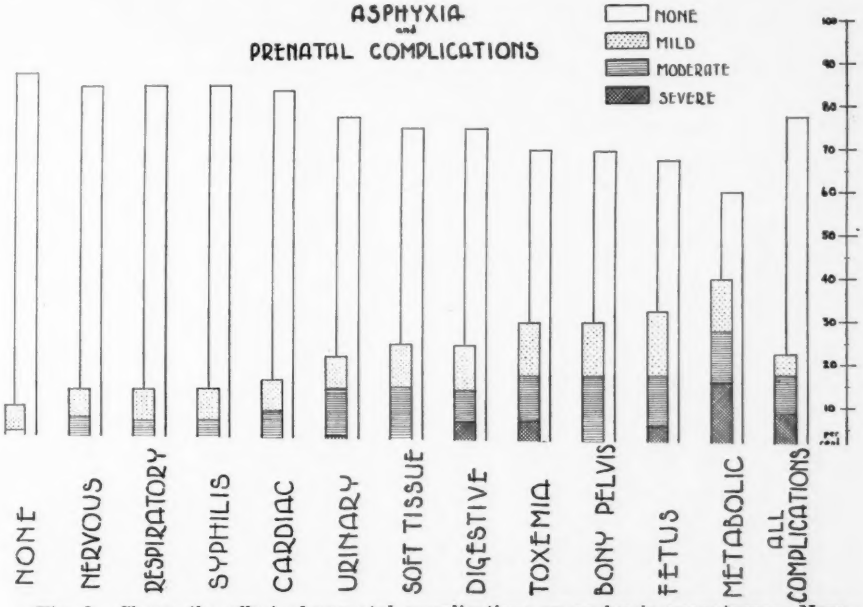


Fig. 2.—Shows the effect of prenatal complications on asphyxia neonatorum. Nervous system complications (35 cases) include paralysis, psychosis and others. Respiratory diseases (69 cases) are minor, such as common cold, and major, such as tuberculosis, bronchitis, and pleuritis. Syphilis 38 cases. Cardiac disease (63 cases) includes all types of heart disease in all stages of compensation. Urinary complications (47 cases) are primarily pyelitis. Soft tissue anomalies (39 cases) are those of the pelvis and include fibroids, cysts, prolapse and others. Digestive disturbances (28 cases) are colitis, appendicitis, cholecystitis, hepatitis, and others. Late toxemias 129 cases. Contracted pelvis 120 cases. Metabolic diseases (18 cases) were either diabetes mellitus or hyperthyroidism.

TABLE II. A COMPARISON OF THE FREQUENCY AND SEVERITY OF ASPHYXIA AND NEONATAL MORTALITY DURING VARIOUS GESTATIONAL AGES

GESTATIONAL AGE IN WEEKS	NO. OF INFANTS	NO ASPHYXIA		MILD ASPHYXIA		MODERATE ASPHYXIA		SEVERE ASPHYXIA	
		% NOT ASPHYXIATED	% OF NEONATAL DEATHS	% OF ASPHYXIA	% OF NEONATAL DEATHS	% OF ASPHYXIA	% OF NEONATAL DEATHS	% OF ASPHYXIA	% OF NEONATAL DEATHS
28	33	48.5	50.0	15	80	30.0	90	6.5	100
32	50	58.0	17.0	18	11	16.0	50	8.0	100
36	177	76.5	3.0	9	0	10.5	20	4.0	43
40	1,655	86.0	1.5	6	0	5.0	10	1.75	66
40+	67	85.5	0.0	8	0	5.0	30	1.5	100

logical method, being well aware of the inaccuracy of gestational age based on menstrual history alone. All infants born before the twenty-eighth week were excluded. Table II shows the incidence of asphyxia and neonatal death in relation to maturity.

Maturity as determined by gestational age has a profound effect on the incidence of asphyxia, and asphyxia in turn is followed by an increase of the neonatal death rate. For example, a 28-week-old infant born without asphyxia has a better chance of survival than a term infant born with severe asphyxia. Asphyxia is increased in the premature following the use of nonvolatile analgesics and is of great importance, as can be seen from Fig. 3. The question of analgesia will be further discussed subsequently.

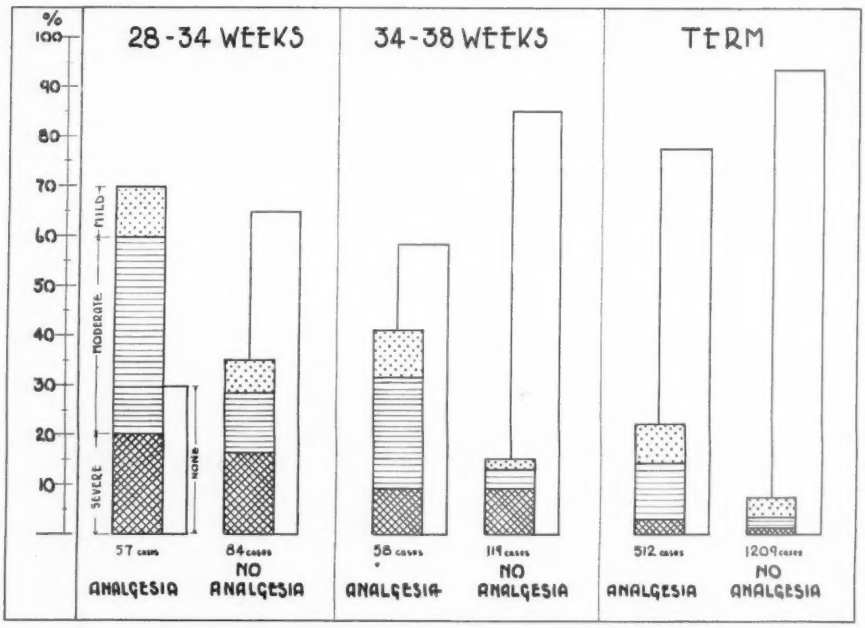


Fig. 3.—Shows the effect of all nonvolatile analgesics, mostly opiates, in relation to maturity. The combination of prematurity and analgesia result in an unusually high percentage of asphyxia neonatorum. The increase is most marked in the moderate and severe degrees.

Presentation and Position.—As would be expected breech presentations were associated with double the incidence of asphyxia found in cephalic presentations, the figures being 27 per cent and 14 per cent, respectively. There was also a relation to position as well. The two occipitoanterior positions, R.O.A. and L.O.A., were practically identical in incidence of asphyxia. All occipitotransverse and posterior

TABLE III. THE RELATION OF ASPHYXIA TO PRESENTATION AND POSITION

POSITION AND PRESENTATION	NO. OF INFANTS	NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE ASPHYXIA
All occipitoanterior positions—L.O.A. and R.O.A.	1334	88.5	6.0	5.0	1.5
All occipitotransverse and posterior positions—L.O.T., L.O.P., R.O.T., R.O.P.	518	81.0	7.0	8.5	3.5
Breech	80	74.5	11.0	9.0	5.5

positions were also similar but in these the incidence of asphyxia was increased 33 per cent and the severe type of asphyxia doubled. The results are summarized in Table III. The results are not surprising when one considers that in this series occipitoposterior positions were accompanied by a threefold increase in incidence of operative delivery, a twofold increase in the administration of nonvolatile analgesics and a 20 per cent and 30 per cent increase in the duration of the first and second stages of labor, respectively. Regardless of the factors that cause the increase in asphyxia, the fact remains that the prognosis for the infant is definitely worse in the case of occipitoposterior and breech presentations.

Duration of Labor.—This is divided into first and second stages as follows: *First stage:* With the exception of precipitate labors and prolonged labors the results are not striking. Because of the marked variation in length of labor in primiparas and multiparas, they are considered separately, yet the results are not significantly different. As can be readily seen from Fig. 4 asphyxia is greatest in labors of less than three to four hours and in those of over thirty hours. The optimum duration of the first stage as regards asphyxia is one of about five to seven

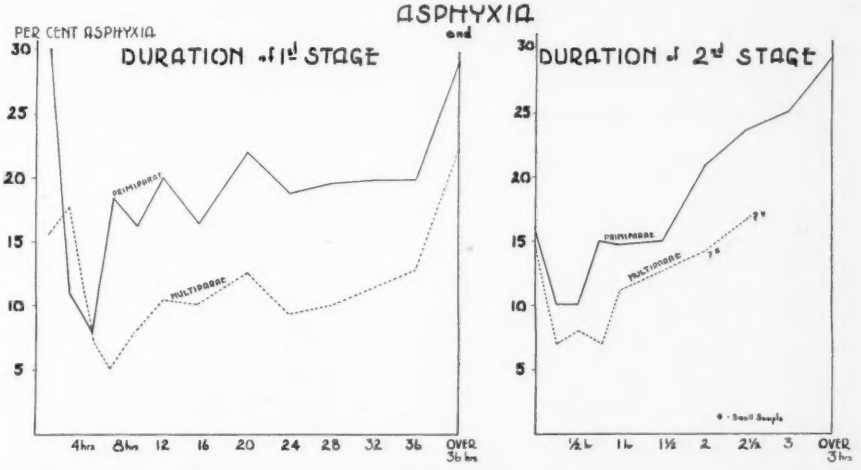


Fig. 4.—Unusually short or prolonged first and second stages result in increased asphyxia neonatorum. The general trend is the same in both primiparas and multiparas. A first stage of over thirty-six hours or a second stage of over one and one-half hours is accompanied by a rapid increase in asphyxia.

hours for both primiparas and multiparas; yet the average duration of the first stage in primiparas was thirteen hours and thirty-six minutes, and 41 per cent of the labors occurred in the nine- to fifteen-hour period. The multiparas had an average duration of the first stage of seven hours and thirty minutes and 42 per cent of the labors took place during the five- to seven-hour period. Thus, multiparas tend to have a first stage of more nearly the optimum duration. Prolonged labor carries a high degree of asphyxia as will be seen under the consideration of complications of labor. *Second stage:* The same general results are observed here. The precipitate deliveries are followed by a mild increase in asphyxia neonatorum but the greater danger follows the long second stage. Comparing the primiparas and the multiparas as before, we find that the primiparas have an average duration of second stage of one hour and seventeen minutes with 46.5 per cent deliveries occurring in the one- and one-and-one-half-hour groups. The average duration in the multiparas was forty minutes, with 69 per cent of the deliveries in the fifteen to forty-five-minute periods. Only 26.5 per cent of the primiparas delivered at the optimum period. Note the relatively rapid increase in the rate of asphyxia after the second stage has exceeded one and one-half hours in length (Fig. 4).

Type of Delivery.—Operative delivery increased asphyxia. Out of 636 operative deliveries 159, or 25 per cent, of the infants had asphyxia, while only 134, or 10 per cent, of those from 1,346 spontaneous deliveries were similarly affected. We recognize that operative delivery is frequently indicated, regardless of the danger of asphyxia, and at times it may actually decrease the incidence of asphyxia when there is a failing fetal heart rate which fails to respond to maternal oxygen therapy,[17] or where there is premature separation of the placenta, prolapse of the cord, or similar disturbances. Table IV shows that operative deliveries per se cause increase in asphyxia neonatorum; for example, the rate of asphyxia in spontaneous deliveries where no nonvolatile analgesics have been given is 8.5 per cent, while following low forceps deliveries under similar circumstances, the rate is 11 per cent. Yet the combination of operative delivery and analgesics greatly increase the incidence and severity of asphyxia.

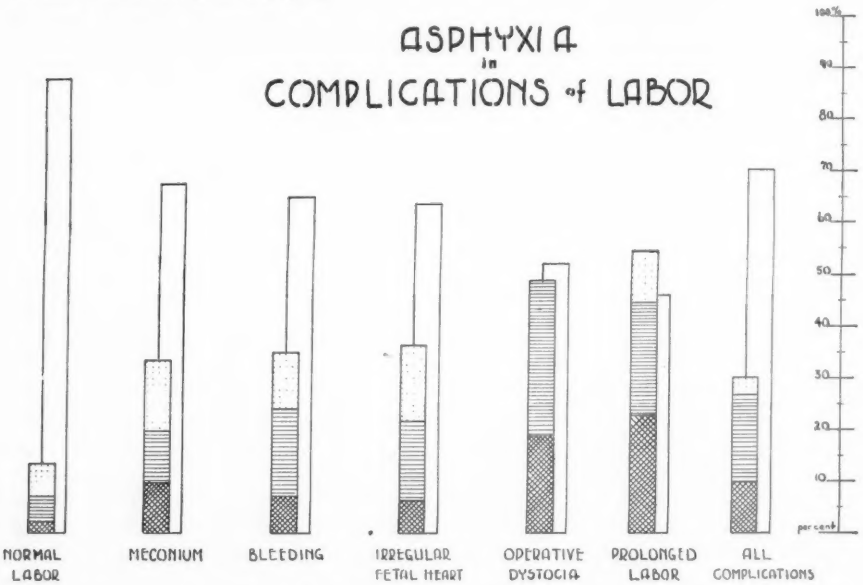


Fig. 5.—Shows some of the dangerous complications of labor in regard to asphyxia neonatorum. Meconium was observed in 37 cases exclusive of breech presentation. Bleeding was noted in 47 cases of placenta previa and premature separation of the placenta. Marked irregularity and slowing of the fetal heart was found in 62 cases. Prolonged labor meant a labor of over thirty-six hours, this present in 26 cases. Operative dystocia was present in 25 cases.

Complications of Labor.—In addition to prenatal complications, we have another group of complications active during labor and more or less intimately associated with it. There were 292 of these cases; however, only 238, or 12 per cent, were of possible effect on the fetus. Those excluded were such factors as post-partum hemorrhage before delivery of the placenta, manual removal of the placenta, and others. Complications of labor include the often mentioned factors of cord prolapse, knots in the cord, and tetanic uterus. These are usually mentioned in textbooks as frequently occurring factors, and one is led to believe that they are responsible for much fetal asphyxia. Actually they occurred in only 5.5 per cent of the 238 complicated labors, or 0.65 per cent of our entire series. When they were present, the incidence of asphyxia was 46 per cent (occult prolapse of cord not included). As will be seen in Fig. 5, there are other complications occurring in greater frequency which are followed by as severe or even more severe asphyxia.

Analgesics.—Unless specifically otherwise stated, the term analgesics is used in this paper to signify drugs other than inhalation analgesics given during labor. The

TABLE IV. A COMPARISON BETWEEN THE TYPE OF DELIVERY, THE USE OF ANALGESICS,* AND THE INCIDENCE AND SEVERITY OF ASPHYXIA

TYPE OF DELIVERY	NO. OF CASES	NO ASPHYXIA %		MILD ASPHYXIA %		MOD. ASPHYXIA %		SEVERE ASPHYXIA %	
		NO ANALG.	WITH ANALG.	NO ANALG.	WITH ANALG.	NO ANALG.	WITH† ANALG.	NO ANALG.	WITH ANALG.
Spontaneous	1,329	91.5	82.5	5.5	6.0	2.0	10.0	0.7	1.0
Low forceps	349	89.0	73.0	5.0	10.5	4.0	13.5	2.3	2.5
Mid-forceps	36	85.5	67.0	0.0	0.0	9.5	33.0	4.5	5.5
Cesarean section	159	78.0	60.0	13.5	11.0	4.0	21.5	4.0	6.5
Breech	80	77.5	68.5	7.5	12.5	7.5	12.5	7.5	8.0
Version	24	44.0	67.0	25.0	0.0	25.0	0.0	6.0	33.0

*Types of analgesics are discussed later.
†Greatest increase in this group.

relationship between analgesics and asphyxia neonatorum has been the subject of much controversial literature for years. It is not the purpose of this paper to discuss the advantages or disadvantages of any of these analgesics as they effect maternal amnesia and pain relief. The relationship of certain of these agents to asphyxia neonatorum will be shown. Recent studies of morphine by Shute and Davis,[10] of barbiturates by Clifford and Irving,[7] and by Lewis,[11] of scopolamine by Cole and associates[6] have summarized the effects of these drugs on asphyxia neonatorum. Our figures tend to confirm some of these observations and in addition present results following the use of heroin. We have deliberately avoided a consideration of the time factor which exists between the time of drug administration and delivery for two reasons: In the first place, it is now well known that the time element is of marked importance in the administration of morphine and closely allied drugs[10] and is of considerable less significance in the case of barbiturates.[7] Second, we always attempt to estimate this time and govern our administration of opiates so that they antecede delivery by at least four hours. In the majority of cases, this is possible. When failures due to inaccurate timing occur, they can be charged to the opiates, because the time factor then becomes a quality of the drug, assuming of course that reasonable obstetric judgment is used in administration. Usually $\frac{1}{12}$ gr. of heroin was the average dose. The morphine dosage varied from $\frac{1}{8}$ to $\frac{1}{4}$ gr. Scopolamine was from $\frac{1}{150}$ to $\frac{1}{200}$ gr., was not repeated, and was used alone only as a premedication for cesarean section. Analgesics administered twelve hours or longer before delivery were excluded. In Table V we find the general results for each of the above-mentioned drugs, included under the title

TABLE V. THE TYPES OF PAIN-RELIEVING DRUGS USED AND THE FREQUENCY AND SEVERITY OF ASPHYXIA NEONATORUM FOLLOWING THEIR USE

TYPE OF DRUG	NO. OF CASES	NO ASPHYXIA %	MILD ASPHYXIA %	MODERATE ASPHYXIA %	SEVERE ASPHYXIA %
None	1,384	89	6.0	3	2.0
Heroin	344	80	7.0	11	2.0
Heroin repeated	47	68	8.5	17	6.5
Morphine alone or with scopolamine	72	70	12.0	12	6.0
Scopolamine*	95	60	13.0	21	6.0
Others	40	87	3.0	5	5.0

*Premedication for cesarean section.

"others" are those who received small doses of barbiturates, codeine, etc., a small heterogeneous group of little significance.

From these figures, it would seem that morphine produces greater asphyxia neonatorum than heroin. A repeat dose of heroin produces about the same asphyxia as does morphine. The increase in asphyxia following heroin occurs in the moderate group; for the remainder, it occurs in the severe groups.

In order to exclude and to evaluate the factor of trauma, we have analyzed the various drugs in relation to spontaneous, low forceps deliveries, and then all operative deliveries in relation to total asphyxia. From Table VI we see that in the case of spontaneous delivery heroin has a definite advantage over morphine, but in the operative deliveries this advantage is lost. Furthermore, there is a definite danger in repeating any opiate, even heroin, though it is known to be one of the most rapidly acting ones.[6] In the same table we have combined the results of various analgesics in the premature infants.

TABLE VI. THE INCIDENCE OF ASPHYXIA IN RELATION TO TYPE OF DELIVERY, MATURITY, AND TYPE OF ANALGESIC

TYPE OF ANALGESICS	NO. OF CASES	PER CENT IN SPONT.	PER CENT IN LOW FORCEPS	PER CENT IN ALL OPERATIVE	PER CENT IN TERM INFANTS	PER CENT IN ALL PREMATURES
None	1,384	8.5	11.0	15	8	22
Heroin	344	16.0	28.5	29	18	40
Heroin repeated	47	22.0	30.5	39	21	64
Morphine alone or with scopolamine	72	31.5	29.5	28	26	50
Scopolamine	95	0	0	40	34	69
Others	40	22.0	10.0	20	6	40

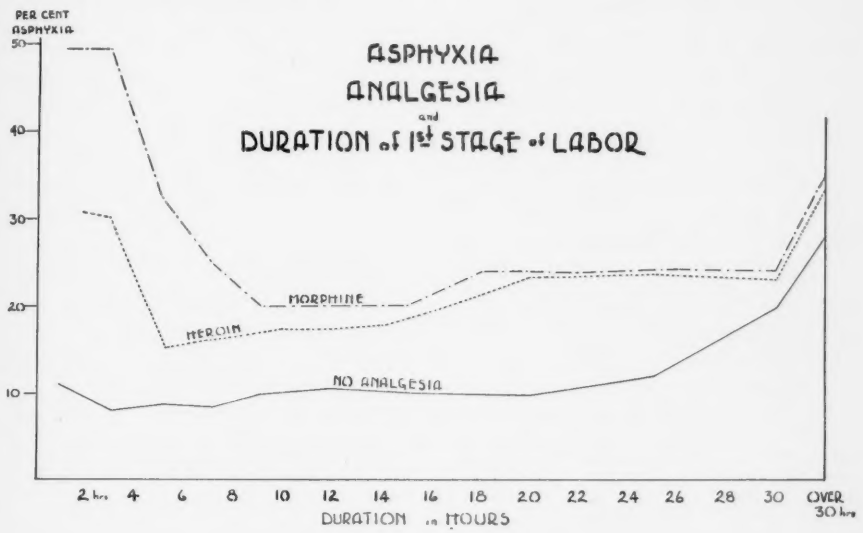
In the relation to maturity, there is apparently no specificity as far as the drugs used were concerned. Asphyxia increased markedly in prematures following all types of analgesics. Space does not permit a complete analysis of maturity and types of asphyxia but the increase occurs in the "moderate" group in the prematures.

One cannot avoid the old question of the interrelationship of asphyxia, length of labor and analgesic drugs, Are they independent, related, or synergistic? We have previously stated that asphyxia increased after rapid labors. However, when these figures are analyzed on a basis of analgesia, we find that only the patients having had analgesics show this effect, while those with no analgesia had no increase in asphyxia following a short first stage (Fig. 6). The asphyxia is due to an error in judgment in administering opiates to patients that deliver within five hours after the onset of labor. Prolonged labor apparently causes increased asphyxia whether analgesics are given or not, but the total figures are too small for accurate interpretation. The situation during the second stage of labor is similar as regards the cases delivering within fifteen minutes, asphyxia being apparently due to analgesia and not to the rapid labor. However, a reversal is noted in relation to prolongation of the second stage. Here asphyxia neonatorum was greater when the mothers were given analgesics. The optimum length of the second stage of labor is about thirty minutes, and at this particular time, there is little difference between those receiving analgesia and those without it.

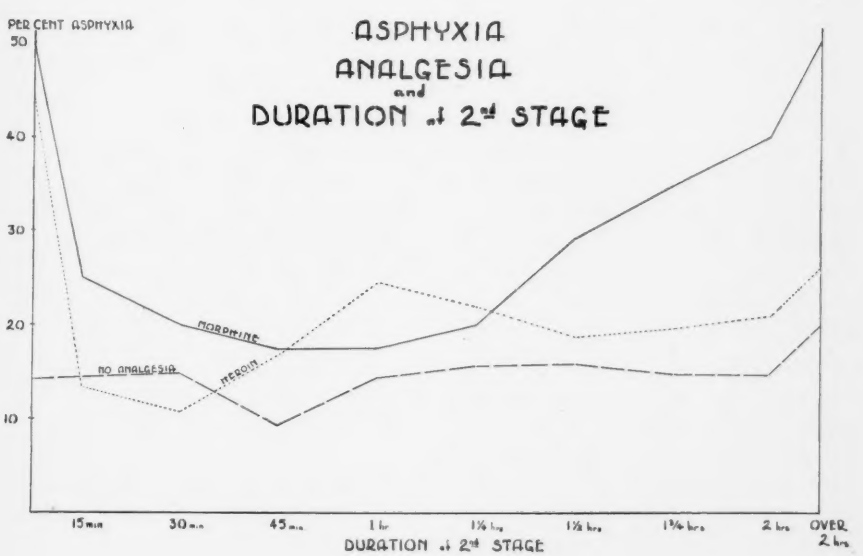
Induction of Labor.—Medical induction of labor, using enemas and quinine, 15 to 30 gr., and posterior pituitary, had apparently little effect on the incidence of asphyxia. Sadler and others[19] described deleterious effects on the infant from quinine given for medical induction. The total asphyxia in our 1,656 noninduced cases was 13.6 per cent and in the 311 medically induced cases was 15 per cent.

Anesthesia and Analgesia.—Of the 1,982 cases 1,806 had some form of inhalation analgesia or anesthesia; 1,504 patients had nitrous oxide-oxygen intermittent analgesia with pains; 142 had no inhalation analgesia or anesthesia; 350 had an-

esthesia without analgesia; and 477 of the 1,504 patients having analgesia had subsequent anesthesia with delivery. A complete study of gas analgesia and anesthesia in relation to asphyxia has been made and will appear in a subsequent publication. In general, the results show that intermittent nitrous oxide-oxygen analgesia properly used is associated with a low incidence of asphyxia neonatorum. General anesthesia as given for operative delivery may be associated with increased asphyxia, that this was not due to trauma alone was demonstrated in the cases of cesarean section where the rate was equally as high.



A.



B.

Fig. 6.—Prolonged labor, both first (*A*) and second stage (*B*), is accompanied by increased asphyxia neonatorum. Rapid labors are not followed by increased asphyxia neonatorum except when heroin or morphine is given for analgesia, in which case delivery occurs before the depressant effects of the drug are lost.

Infant Complications.—Exclusive of congenital malformations, 41.5 per cent of the asphyxiated infants had some type of postnatal complication, while only 17 per cent of the nonasphyxiated babies had complications. These were all inclusive in their nature, such as trauma, both major and minor; all types of respiratory infections, atelectasis, cough, mucus, etc.; excessive regurgitation; unusual irritability or lethargy, etc. We were able to follow over half the infants for one year or longer, and in this group, there were 10 with permanent central nervous defects, of which 4 had severe asphyxia at birth and one had moderate asphyxia. One striking case can be mentioned: An elective cesarean section was done at term before onset of labor in a patient with contracted pelvis but otherwise normal. Technical difficulties encountered during anesthesia were responsible for severe anoxia of the mother and fetus; the infant was deeply asphyxiated at delivery and had a stormy postnatal course. Later encephalograms revealed a generalized cortical atrophy, and because of mental deficiency, the infant was institutionalized.

DISCUSSION

For many years it has been customary to classify surgical patients as to their surgical risk; and on this basis, the choice of surgical procedure, the method of anesthesia, and type of premedication are made. This classification has not been in general use in obstetrics where the complexities of the problem are multiplied by the necessity of evaluating two patients, mother and baby. In the past, the mother has usually received the major portion of the attention, frequently at the unnecessary expense of the fetus. There is an unfortunate tendency to generalize in the treatment of obstetric patients. Such statements as "I give all my primiparas morphine, ¼ gr.," "all multiparas receive 6 gr. of nembutal" or "all primiparas are delivered by forceps with ether anesthesia" are frequently made. Complete individualization should be the rule, not only for the mother but also for the fetus. Only by combining our knowledge of these two factors in their proper relation can we arrive at a rational course of therapy. The proper proportions between factors that favor the safety and comfort of the mother but endanger the fetus can be determined only by obstetric judgment.

Just as the mother is evaluated as an obstetric risk, so should the fetus be considered from the standpoint of *asphyxial risk.* There are many factors that increase the incidence of asphyxia neonatorum. On the basis of frequency and severity, we have found them to be prematurity, especially when combined with nonvolatile analgesics; prenatal complications, particularly toxemias, hyperthyroidism, diabetes, contracted pelves, multiple pregnancy, hydramnios, pyelitis, and pelvic soft tissue abnormalities. The most dangerous complications of labor are prolonged labor, operative dystocia, placenta previa, and premature separation of the placenta, irregularities of the fetal heart rate. Operative delivery causes some increase in asphyxia, but when combined with opiates greatly increased the asphyxia. From the nature of these etiologic factors, it is obvious that good prenatal care is a potent factor in limiting asphyxia neonatorum. Prematurity and various prenatal complications need to be promptly recognized and treated. The remainder of the problem can be improved by individualizing the conduct of labor both as it affects the mother and the infant in utero. The diagnosis of fetal anoxia in utero by fetal heart arrhythmia and treatment by maternal oxygen administration should be kept in mind.[17]

SUMMARY AND CONCLUSIONS

The rational approach to the problem of asphyxia neonatorum is by prophylaxis, notwithstanding the voluminous literature concerned with therapeutic methods. Analysis of the etiologic factors of asphyxia as seen in 2,006 consecutively born infants reveal the following:

1. *Parity:* Primiparas had 18.9 per cent asphyxiated babies while the multiparas had 11 per cent, but after the eighth child asphyxia increased with parity.

2. *Prenatal Complications:* Their presence increased asphyxia from 11 per cent in the uncomplicated to 26 per cent in the complicated cases. Metabolic diseases, soft and bony pelvic abnormalities, toxemias, multiple pregnancy, and diseases of the gastrointestinal and urinary tracts were followed by the greatest incidence of asphyxia.

3. *Prematurity:* The greatest single factor in our series, most dangerous when combined with analgesic drugs where as high as 70 per cent asphyxia was found.

4. *Presentation and Position:* Breech presentation was followed by 27 per cent asphyxia, occiput posteriors by 18.2 per cent, and occiput anteriors by 12.2 per cent asphyxia.

5. *Duration of Labor:* Only when the first stage was over thirty hours was there a marked increase in asphyxia. A second stage of over one and one-half hours was followed by a progressive increase in asphyxia.

6. *Type of Delivery and Trauma:* Spontaneous deliveries showed a rate of 10 per cent asphyxia while operative deliveries were followed by 25 per cent asphyxia. Use of nonvolatile analgesics before operative delivery greatly increased asphyxia.

7. *Complications of Labor:* Variations in rate and rhythm of the fetal heart, maternal bleeding, cord prolapse, operative dystocia, and prolonged labor were accompanied by asphyxia neonatorum varying from 35 to 55 per cent. Uncomplicated labor resulted in 12 per cent asphyxiated infants.

8. *Analgesics:* Analgesics studied were primarily heroin and morphine with or without scopolamine. In spontaneous deliveries heroin stood midway between the group receiving no sedation and those receiving morphine. This advantage was lost following operative deliveries. Repeated administration of heroin was followed by increased asphyxia in spite of its rapid action.

9. *Medical Induction of Labor:* This had little effect on asphyxia.

10. *Infant Complications:* They increased from 17 per cent to 45 per cent when the infant was asphyxiated at birth. Ten cases of permanent central nervous system damage were found; five of these infants had asphyxia at birth.

The individual evaluation of every obstetric case on the basis of fetal asphyxial risk, as well as a general obstetric risk, is advised. Prenatal care and conduct of labor on this basis should result in a substantial reduction of the incidence of asphyxia neonatorum.

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THE VALUE OF CALCIUM IN LABOR AND IN UTERINE INERTIA*

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INVESTIGATION of the effects of the intravenous administration of calcium salts in labor was undertaken for two reasons: First, we questioned whether calcium might relieve the pain of uterine contractions; and, second, we wished to determine the effect of calcium on the contractibility of the human uterus during labor.

The basis for the speculation that calcium might relieve the pains of labor was the relief of pain that had been obtained by means of this treatment in lead colic,[4] gallstone colic,[22] acute epididymitis,[23, 35] acute salpingitis,[30] and certain malignant conditions.[5] Muscle cramps which occur during pregnancy commonly yield readily to calcium administered orally.[17, 18, 26, 32] Hence, it seemed reasonable to suppose that calcium might relieve the spasmodic uterine pain of labor, thus permitting the uterus to contract painlessly, as do other muscles of the body. The mechanism of the action of calcium on the body tissues may be explained by the statement that it decreases the permeability[11, 13] of cells and thus lessens the excitability of striated and smooth muscles and also somatic and autonomic nerves. Since it is known that section of the presacral (sympathetic) nerve plexus will relieve pain caused by the contracting uterus during labor,[16] it was hoped that calcium, by reducing the excitability of the sympathetic nerves, might have a similar effect. Empirically, calcium has been used as one of the agents for the relief of dysmenorrhea. Kraus and Zondek, on the other hand, have reported that an excess of calcium in the body will produce certain effects similar to those produced by stimulation of the sympathetic nerves. If this is true, calcium would not relieve the pains of labor. Hartley[17, 18] wrote that the oral administration of calcium to a woman during pregnancy would definitely shorten the period of labor. Richardson[32, 33] showed that viosterol administered during pregnancy would increase the value for calcium in the blood and that such a procedure would subsequently result in a shortening of the average

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labor of primiparas of from nineteen hours to six hours. Bacq and his associate, in studies on cats, demonstrated that the administration of calcium would cause contraction of the denervated, nonpregnant uterus, but that such contraction would occur only when the adrenal vessels were ligated. After the injection of ergotamine had depressed intestinal muscles so that contractions no longer occurred, the administration of calcium permitted subsequent doses of ergotamine to stimulate the intestine again, according to Salant and Parkins. Rozen and Perussé observed effects similar to those experienced with ergotamine and calcium by administering magnesium chloride and calcium lactate orally. Calcium chloride administered intravenously, however, caused loss of intestinal tonus and vomiting. They thought these actions to be central effects, because contraction of strips of gastric muscle has been shown to be enhanced when such strips are immersed in a solution of calcium. Berg and associates said Billingheimer noted that the administration of epinephrine (which slows or stops uterine contractions[9]) would decrease the value for calcium in the blood. This action could be interpreted to mean that an increase in the content of calcium in the blood might increase uterine contractions. Fitzhugh and associates, searching for the pain-relieving mechanism of calcium in spasm of smooth muscle, found that calcium lessens intestinal motility, but does not stop it. Johnson injected calcium gluconate, both intravenously and intramuscularly, into nonpregnant, ovariectomized rabbits that had received daily doses of a preparation which contained estrogenic hormone. The intensity and frequency of the uterine contractions were increased. Danforth and Ivy, in studies on dogs and rabbits after they had given birth to young, determined that calcium not only stimulates the uterus, but that its presence is necessary for the stimulating effect of the oxytocic principle of the posterior lobe of the hypophysis (pitocin), ergonovine, and histamine. Wiessmann and Klippel said that Pieri administered calcium gluconate to a woman in labor and noted that labor terminated more rapidly than in other patients in whom calcium gluconate had not been employed. This is the only record we can find of the administration of calcium to a woman in labor, with the exception of the work of Bardenheuer, who did employ calcium but did not mention the effect of it on uterine contractions. Winkler and Vetter used a mixture of calcium and quinine in an attempt to induce labor.

MATERIAL

The 26 pregnant women who were observed in this study were on a private and semiprivate obstetric service. They were at or near term and were either in labor or were undergoing attempted induction of labor. These conditions made it impossible to complete observations concerning every patient. Calcium gluconate* was used exclusively in this work, because it is less irritating locally than other calcium salts.

METHOD

At first, calcium gluconate was administered when the patient complained of severe uterine pain. Later in the study the drug was administered when it appeared that the uterine contractions were ineffectual, infrequent, short, or weak. In 11 of the 26 cases, a graphic tracing was obtained of the uterine contractions, both before and after the administration of calcium. The tracing was made on a smoked-drum kymograph by a stylus activated by a tambour. Rubber tubing connected the tambour to an air-filled balloon placed on the patient's abdomen over the region of the uterine prominence. A snug abdominal binder provided counterpressure to the balloon. It was necessary for the patient to remain on her back so that a good tracing might be obtained. The kymograph was run for several minutes to make certain that uterine contractions were not affected by the binder. A tracing of the uterine contractions of Patient 14 (Tables I, II, and III) is shown in Fig. 1, and a similar tracing concerning Patient 19 (Tables I, II, and III) is shown in

*Supplied through the courtesy of Abbott Laboratories and of the Sandoz Chemical Works, Inc.

Fig. 2. After completing this work, we learned of the Lorand tocograph and of the excellent tracings of uterine contractions which Murphy obtained with this device. Before calcium was administered, a final check was made of dilatation of the cervix (by rectal examination), blood pressure, pulse, and respiration (Table I). A sample of blood was then drawn from the median basilic vein for determination of calcium. With the needle still in place, the syringe containing a 10 per cent, or sometimes, a 20 per cent, solution of calcium gluconate was attached, and slow administration of the solution was begun. Four cubic centimeters per minute was considered to be the maximal rate at which the solution could be administered with avoidance of un-

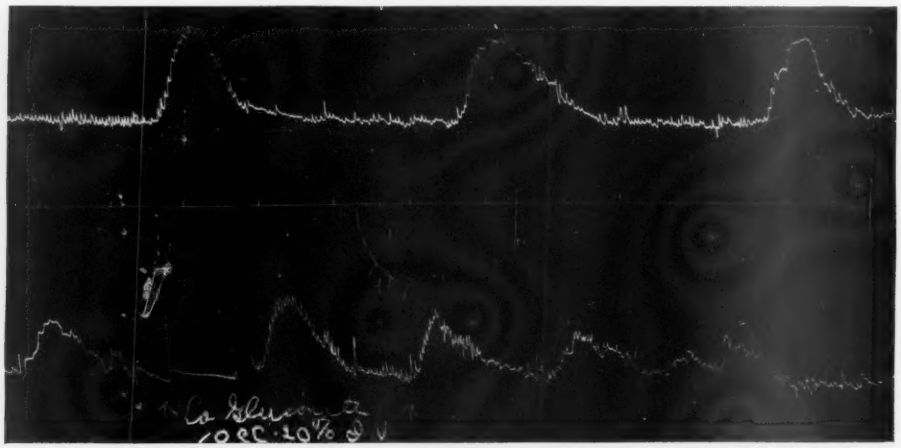

Fig. 1.—Reproduction of a kymographic tracing of the uterine contractions of Patient 14 (Table II) before and after the administration of 10 c.c. of a 20 per cent solution of calcium gluconate. The two lower lines are immediate continuations of the two upper lines. Large curves represent uterine contractions; frequent, small excursions represent abdominal respiratory movements. The decreased interval occurring between uterine contractions after administration of calcium gluconate is clearly shown.

Fig. 2.—Reproduction of a kymographic tracing of the uterine contractions and occurrence of labor pains of Patient 19 (Table II) before and after the administration of 25 c.c. of a 10 per cent solution of calcium gluconate. Large curves represent uterine contractions and each x at the upper margin of the tracing indicates occurrence of a subjective labor pain. Immediate increase in the frequency of uterine contractions after the administration of calcium gluconate is evident.

pleasant side reactions. The dose to be administered was problematic. Certainly, the investigator would hesitate to use the dose that has been used in experiments with animals: 10 to 30 mg. of calcium ion per kilogram of body weight. The lethal dose of calcium, injected intravenously in the form of an 8.4 per cent solution of calcium gluconate, at the rate of 4 c.c. per minute, is 185 ± 57 mg. of calcium ion per kilogram of weight of the animal.[25] Actually, from 1.24 to 5.08 mg. of calcium ion per kilogram of body weight was used in the present study (Table II). Transposed into terms of calcium gluconate, these values would vary from 10 c.c.

of the 10 per cent solution, to 20 c.c. of the 20 per cent solution. Five minutes after the solution had been administered, the blood pressure and the pulse and respiratory rates were again checked, because the maximal changes in these factors are reputed to occur at this time (Table I). With a fresh, sterile needle and syringe a second sample of blood was taken for purposes of determination of calcium five to thirty minutes after the calcium had been injected. From one to eight hours later (usually four hours), a third specimen of blood was obtained for determination of calcium. Making of the tracing was continued for about one hour after the injection of calcium. The content of calcium in the blood was determined by means of the Clark-Collip modification of the Kramer-Tisdall method. Duplicate tests were performed on each specimen of blood.

RESULTS

Effect of Calcium Gluconate on Labor Pains and Uterine Contractions.—No relief of labor pains resulted from the injection of calcium. In fact, in many instances the intensity of the pain was increased.

The effect on uterine contractions was one of stimulation. Twenty-four of the 26 patients experienced an increase in the frequency of contractions. Fifteen of the 26 patients experienced an increase in the intensity of the contractions, and this number includes one patient for whom the contractions did not increase in frequency. The duration of each contraction was not changed much from what it is in the average labor. In no case did tetanic spasm of the uterus occur, such as frequently results from the administration of injudicious doses of the oxytocic principle of the posterior lobe of the hypophysis.

Four cases will be reported herein to depict the decided effect which may be obtained by the administration of calcium.

REPORT OF CASES

CASE 1.—The patient (No. 1 in Table III) was 45 years old. She had had four children. When the patient's cervix was dilated to 9 cm. and the infant's head was 2 cm. above the ischial spines in the left occipital transverse position, uterine contractions became weak. Each contraction lasted forty seconds, and the interval between contractions was five minutes. The patient was prepared for delivery and administration of a 20 per cent solution of calcium gluconate was begun; but, after only 4 c.c. had been given, the uterus contracted strongly for sixty seconds. After an interval of one minute another strong contraction occurred. These two contractions were sufficient to bring the infant down to and over the perineum in the left occipital anterior position.

CASE 2.—The patient (No. 18 in Table III) was 29 years old. She had had one child. She was experiencing pains that occurred every three to four minutes and lasted thirty to eighty seconds at the time that treatment was begun. The cervix was dilated to 3 cm. at the time 15 c.c. of a 20 per cent solution of calcium gluconate was administered. The contractions immediately began to increase in frequency, so that one occurred every one to one and one-half minutes. Each contraction lasted thirty to sixty seconds. Five minutes after the administration of calcium, the patient's cervix was dilated to a diameter of 8 cm. Spontaneous delivery of the child occurred one hour after calcium had been administered.

CASE 3.—The patient (No. 20 in Table III) was 25 years old. She had had one child. She was experiencing adequate uterine contractions every two minutes, and the duration of each contraction was thirty-five seconds. The cervix was dilated to 3 cm. Since this patient was encountered early in the series, at a time when the stimulating effect of calcium was not so well appreciated as it was later, she received 25 c.c. of a 10 per cent solution of calcium gluconate. Contractions immediately

began to occur every minute. They lasted for sixty seconds, with increased intensity. Five minutes later cervical dilatation was complete. Spontaneous delivery of the infant occurred fifteen minutes after the administration of calcium.

CASE 4.—The patient (No. 24 in Table III) was 36 years old. She had had one child. She had been in labor eleven and one-half hours, and was experiencing weak, irregular contractions lasting sixty to 120 seconds, and occurring at intervals of five to nine minutes, when treatment was initiated. The infant's head was in the left occipital transverse position and the patient's cervix was dilated to 3 cm. Immediately after the administration of 20 c.c. of a 20 per cent solution of calcium gluconate, the contractions became strong, occurred every minute, and each contraction lasted sixty to seventy-five seconds. Spontaneous delivery of the child occurred two hours after calcium had been administered.

DISCUSSION

Twenty-three of the 26 patients experienced definite stimulation of the uterus, in the form of an increase in either frequency or intensity of contractions, or both, following the administration of calcium gluconate. One of the 26 patients (No. 5 in Table III), experienced no increase in stimulation of the uterus over that degree of stimulation which, commonly, would have occurred had she not received calcium gluconate. There was no change in uterine contractions after the administration of calcium, and the content of calcium in the blood did not increase twenty-six minutes after such administration. However, the intensity of uterine contractions increased markedly forty-five minutes after the injection of calcium and delivery of the child occurred spontaneously five hours later. The increase in uterine contractions was so transitory in two cases that it could not be considered a true stimulation. One patient (No. 15 in Table III) was not in labor; Braxton Hicks' contractions increased after injection of calcium, but she experienced no true labor pains. Another patient (No. 25 in Table III) also was not in labor. The medical induction of uterine contractions by means of castor oil and ten injections of the oxytocic principle of the posterior lobe of the hypophysis (pitocin), 2 minims at each injection at thirty-minute intervals, had been completed four hours previously, and she was experiencing mild pains every five minutes at the time we began treatment. After she had received calcium, the pains increased in frequency so that they occurred every three minutes, but they ceased after fifteen minutes. The value for calcium in the blood was low and did not increase much (Table II).

Of the 23 patients in whom treatment was successful, the increase in contractions was short lived in three. For the first patient (No. 6 in Table III) the increased contractions became irregular after the administration of 1½ gr. (0.1 Gm.) of pentobarbital sodium. In the second patient (No. 8 in Table III), after the cervix had been dilated to a diameter of 6.5 cm., the increased contractions ceased for a period of eleven hours, after the administration of 3 gr. (0.2 Gm.) of pentobarbital sodium. The third patient (No. 16 in Table III) was not in labor. Uterine contractions increased for one and one-half hours, then decreased again and finally stopped.

In four additional cases of the 23 patients in whom treatment was successful, no progress toward the desired objective was noted, despite

the increase in uterine contractions. For two patients (No. 11 and 22 in Table III) manual rotation of the occiput from posterior to the anterior position was done, and the child was delivered by extraction with forceps. For the third patient (No. 23 in Table III), extraction of the infant with low application of forceps was done, with a moderate amount of difficulty. The infant of the fourth patient (No. 17 in Table III) was delivered by means of cesarean section because of pelvic-fetal disproportion. In none of these cases in which birth of the infant was obstructed did the administration of calcium seem to do harm.

In the remaining 16 cases of the 23 in which the administration of calcium was successful in increasing the effectiveness of uterine contractions, the patients progressed uneventfully to parturition after the injection of calcium. Of these patients, 13 were delivered within four hours and one each was delivered in five, seven, and nine hours, respectively. All but one gave birth to infants spontaneously. For the one who did not, delivery with the low application of forceps was done because of slowing of the fetal heart.

General Systemic Effects of Calcium Gluconate.—No marked systemic effect was observed after the administration of calcium. Five of the 26 patients regurgitated the gastric contents during injection

TABLE I. ADMINISTRATION OF CALCIUM GLUCONATE TO 26 PREGNANT WOMEN: DOSAGE OF DRUG AND VALUES FOR BLOOD PRESSURE, PULSE AND RESPIRATION RATES AT AND AFTER ADMINISTRATION

PATIENT	CA. ION, MG. PER KG. BODY WEIGHT	REGURGITATION	BLOOD PRESSURE MM. OF HG		PULSE RATE PER MIN.		RESPIRATION, RATE PER MIN.	
			A*	B†	A*	B†	A*	B†
1	1.24	No	–	–	–	–	–	–
2	1.25	No	130/90	–	98	–	24	–
3	1.92	Yes	–	136/88	–	80	–	20
4	2.18	No	120/75	120/90	76	64	16	18
5	2.24	No	132/98	–	96	–	24	–
6	2.50	No	108/82	104/84	86	88	24	20
7	2.69	No	140/100	150/90	72	60	20	18
8	2.82	No	122/80	122/68	74	77	18	19
9	2.85	No	110/65	114/70	80	64	20	20
10	2.96	No	110/78	136/80	84	86	18	18
11	2.96	No	110/88	–	100	–	24	–
12	3.02	No	114/86	–	104	–	24	–
13	3.05	Yes	128/88	155/110	70	88	19	20
14	3.05	No	134/70	126/80	100	100	24	22
15	3.22	No	128/90	146/106	84	78	16	18
16	3.26	No	112/76	130/80	74	64	15	16
17	3.26	No	136/94	142/96	90	76	20	24
18	3.40	No	120/80	130/90	92	–	20	–
19	3.57	Yes	122/76	–	82	–	18	–
20	3.75	Yes	144/92	130/84	79	74	19	17
21	4.04	No	108/80	102/72	84	80	18	16
22	4.30	No	–	–	–	–	–	–
23	4.50	No	126/56	134/72	92	88	16	22
24	4.66	Yes	128/90	150/96	100	80	20	18
25	4.89	No	135/95	135/98	88	88	22	28
26	5.08	No	114/80	120/80	76	66	14	12

*A, At time of injection.
†B, Five minutes after injection.

(Table I), but even these patients experienced little nausea. Regurgitation was not considered to be an indication for discontinuance of injection of calcium.

The regurgitation which 5 of the 26 patients experienced (Table I) was accompanied by audible peristaltic sounds. This effect passed off rapidly. In no case did it persist after the needle had been withdrawn from the vein. Fitzhugh and associates noted that administration of calcium did not relax induced intestinal spasm in dogs, but that it did modify the peak of the spasmodic contractions. In its effect on the 5 patients who experienced regurgitation, calcium probably stimulated the intestinal muscle somewhat in the same manner that it does the uterine musculature.

Effect of Calcium Gluconate on Blood Pressure, Pulse, and Respiration.—In general, systolic and diastolic blood pressures and pulse pressure tended to show an increase when readings were made five minutes after injection of calcium (Table I). The rate of respiration did not change more than six per minute for any patient, and the increase and decrease was distributed approximately equally. Variation in the blood pressure and pulse after the injection of calcium was as inconclusive as that published by other investigators.[4, 24, 39] Among those of our 26 patients concerning whom complete readings of blood pressure and pulse and respiratory rates were obtained (Table I), the change in systolic blood pressure varied from –14 to +27, and the average was +6.7, expressed in millimeters of mercury. Similarly, the change in diastolic blood pressure varied from –12 to +22, and the average was +4.4, expressed in millimeters of mercury. The change in pulse pressure varied from –14 to +24, and the average was +3.3. The change in the pulse rate varied between –20 and +12, and the average was –5.2, expressed in beats per minute. It is likely that labor pains modified these readings somewhat, although we attempted to take the readings in the intervals between pains. Another factor was the dosage employed. Lieberman, who administered 35 to 40 mg. of calcium ion per kilogram of body weight to dogs, wrote that there resulted a decrease of 20 to 40 beats per minute in pulse rate, and an increase of 20 mm. of mercury in systolic blood pressure. Our readings, however, concerned human beings who received from 2.18 to 5.08 mg. of calcium ion per kilogram of body weight.

A vasomotor wave, characterized by the subjective feeling of warmth in the patient's skin, could be induced at will by rapid injection of solution of calcium gluconate. This symptom was not a cause for complaint if the rate of injection was 4 c.c. per minute, or less, of the 10 per cent solution.

Effect of Calcium Gluconate on Blood Chemistry.—The effect of the injection of calcium upon the content of calcium in the blood was not constant. Whether or not results would be the same if calcium were administered to nonpregnant women, it would be difficult to predict. It increased during the first few minutes (five to thirty minutes) after injection of calcium in nineteen of 20 cases in which determinations were made both before and five to thirty minutes after such injections (Column B in Table II). The increase, however, was not proportional

TABLE II. ADMINISTRATION OF CALCIUM GLUCONATE TO 26 PREGNANT WOMEN: WEIGHT OF PATIENTS, AMOUNTS AND SOLUTIONS EMPLOYED, AND CALCIUM CONTENT OF THE BLOOD AT AND AFTER ADMINISTRATION

PATIENTS		CALCIUM GLUCONATE			BLOOD CALCIUM, MG. PER 100 C.C. OF BLOOD				
NO.	BODY WT., KG.	SOLUTION, C.C.	SOLUTION, PER CENT	CALCIUM ION, MG. PER KG. BODY WEIGHT	A†	B†	C†	INCREASE	
								ACTUAL	THEORETIC
1	58.2	4	20	1.24	–	–	–	–	1.61
2	71.8	10	10*	1.25	–	–	–	–	1.63
3	93.6	20	10	1.92	10.4	12.2	12.7	1.8	2.50
4	57.7	14	10	2.18	10.8	11.8	11.4	1.0	2.84
5	80.5	20	10	2.24	9.8	9.8	9.6	0.0	2.91
6	71.8	20	10	2.50	9.3	11.1	9.8	1.8	3.26
7	66.8	20	10	2.69	10.6	11.6	–	1.0	3.50
8	63.6	20	10	2.82	–	–	–	–	3.68
9	63.1	20	10	2.85	8.51	9.5	–	0.99	3.71
10	81.8	27	10	2.96	6.6	7.8	7.6	1.2	3.85
11	79.1	13	20	2.96	8.71	10.1	–	1.39	3.85
12	74.5	25	10	3.02	9.3	11.1	10.3	1.8	3.94
13	59.0	20	10	3.05	9.1	11.8	–	2.7	3.96
14	59.1	10	20	3.05	9.7	10.7	–	1.0	3.96
15	55.9	20	10	3.22	8.6	9.6	–	1.0	4.19
16	69.1	25	10	3.26	9.5	–	–	–	4.24
17	82.7	15	20	3.26	9.5	10.9	8.9	1.4	4.24
18	79.5	15	20	3.40	9.5	–	10.3	0.8	4.42
19	63.1	25	10	3.57	10.5	11.1	10.4	0.6	4.64
20	60.0	25	10	3.75	10.4	11.4	11.2	1.0	4.87
21	66.8	15	20	4.04	8.5	10.4	9.2	1.9	5.25
22	62.7	15	20	4.30	8.68	11.4	–	2.72	5.60
23	60.0	15	20	4.50	9.3	10.9	–	1.6	5.85
24	77.2	20	20	4.66	–	–	–	–	6.06
25	57.3	16	20	4.89	7.5	8.3	–	0.8	6.36
26	53.2	15	20	5.08	8.51	9.9	–	1.39	6.60

*Calcium-quinine.

†A, At time of injection; B, five to thirty minutes after injection; C, one to eight hours after injection.

to the amount of solution injected, or to the quantity of solution of calcium gluconate injected per kilogram of body weight. Actual increase expressed in milligrams of calcium per 100 c.c. of blood varied from 0 to 2.72 and the average increase would be slightly in excess of 1.32, based on calculation for 21 patients, and not all 26 of the series (Table II). The theoretic increase in calcium in the blood (Table II), if it were assumed that all the calcium remained in the blood stream a few minutes after the injection, would be the number of milligrams of calcium ions injected per 100 c.c. of blood. This theoretic increase in calcium in the blood was calculated by utilization of the estimated figure of 1:13[37] as the ratio of the volume of blood in liters to the weight of the body in kilograms. In Table II it is seen that among all 26 patients, the theoretic increase in calcium in the blood varied from 1.61 to 6.60 mg. per 100 c.c. Basis for this calculation follows:

$$\text{Mg. calcium gluconate injected} \times \frac{9 \text{ calcium ions}}{100 \text{ calcium gluconate}} = \text{Mg. calcium ions injected.}$$

$$\frac{\text{Mg. calcium ions injected}}{\text{Patient's weight in kg.}} \times \frac{13 \text{ body weight}}{1 \text{ blood volume (liters)}} = \text{Mg. calcium ions injected per liter of blood.}$$

$$\text{Mg. calcium ions injected per liter of blood} \times \frac{1 \text{ liter}}{10 \text{ (100 c.c.)}} = \text{Mg. calcium ions injected per 100 c.c. of blood.}$$

TABLE III. ADMINISTRATION OF CALCIUM GLUCONATE TO TWENTY-SIX PREGNANT WOMEN: DOSAGE, VALUES FOR BLOOD CALCIUM, DILATATION OF CERVIX, PARITY OF PATIENTS AND UTERINE CONTRACTIONS RESULTING*

PATIENT	CERVIX DILATED TO, CM.	PARITY	MG. CA. PER KG. BODY WEIGHT	BLOOD CA., MG. PER 100 C.C.		UTERINE CONTRACTIONS					
						FREQUENCY, MIN.		DURATION, SEC.		INTENSITY	
				A	RISE	A	B	A	B	A	B
1	9	4	1.24	–	–	5	1	40	60	Wk.	Str.
2	4½	1	1.25	–	–	2-3	1½-2	35	35	Wk.	Str.
3	2	1	1.92	10.4	1.8	3½	2½	45	45	Str.	Str.
4	2	0	2.18	10.8	1.0	2	2	45	45	Mod.	Str.
5	6	0	2.24	9.8	0.0	2	2	75	75	Mod.	Mod.
6	3	1	2.50	9.3	1.8	3½	3	30	40	Wk.	Mod.
7	3	1	2.69	10.6	1.0	3	¾-1	30	30	Str.	Str.
8	3	1	2.82	–	–	5-10	1½	10	30	Wk.	Str.
9	4	2	2.85	8.51	0.99	3½	3½	60	60-90	Mod.	Str.
10	2	2	2.96	6.6	1.2	3	1½	30-75	60	Mod.	Str.
11	10	1	2.96	8.71	1.39	3-5	2	30	30	Mod.	Mod.
12	9	1	3.02	9.3	1.8	6-7	2½-3	45-60	30	Mod.	Str.
13	4	0	3.05	9.1	2.7	3	2	45	45	Str.	Str.
14	1	1	3.05	9.7	1.0	2½	1	75	75	Str.	Str.
15	0	1	3.22	8.6	1.0	10	5	20	20	Wk.	Mod.
16	0	1	3.26	9.5	–	3-12	4	45	60	Wk.	Mod.
17	0	0	3.26	9.5	1.4	3-6	½-1½	60-120	60-120	Str.	Str.
18	4	1	3.40	9.5	0.8	3-4	1-1½	30-80	30-60	Mod.	Str.
19	5	0	3.57	10.5	0.6	3-3½	½-1½	50	50	Mod.	Str.
20	3	1	3.75	10.4	1.0	2	1	35	60	Mod.	Str.
21	0	2	4.04	8.5	1.9	3-4	2-3	75-120	75-120	Str.	Str.
22	9	2	4.30	8.68	2.72	2-3	1½	30	30	Mod.	Mod.
23	10	0	4.50	9.3	1.6	5½	1½-3½	60	30-60	Mod.	Str.
24	3	1	4.66	–	–	5-9	1	60-120	60-75	Wk.	Str.
25	1½	0	4.89	7.5	0.8	5	3	40	40	Mod.	Mod.
26	2	2	5.08	8.51	1.39	2-10	1-2	60-120	30-120	Mod.	Mod.

*A, At time of injection. B, Five to thirty minutes after injection. Wk., weak; Mod., moderate; Str., strong.

The effect of calcium on uterine contractions was not proportional to the amount of calcium injected per kilogram of body weight, or to the actual increase in calcium in the blood after the injection of calcium. Values for calcium in the blood corresponded to those found to exist during labor by other workers,[1, 7, 8, 20, 27-29, 33] but the value for calcium in the blood after the injection of calcium did not increase more than 2.72 mg. per 100 c.c., in contrast to greater increases observed by workers in experimental laboratories in similar studies.[11, 12, 24, 38]

A few patients complained of a sensation of faintness and of profuse perspiration during injection of the calcium. Reductions of values for blood sugar of from 10 to 31 mg. per 100 c.c. within five to fifteen minutes by the intravenous injection of calcium salts have been reported. The sensation of faintness and complaint of profuse perspiration previously mentioned may be referable to the temporary presence of hypoglycemia. The symptoms disappeared after the injection had been completed, and in no case was it necessary to cease administration. Administration of calcium was discontinued for thirty to sixty seconds, however, as a precautionary measure.

Effect of Calcium Gluconate on Newborn Infants.—None of the babies born to these 26 mothers exhibited any ill effects referable to the administration of calcium.

CONTRAINDICATIONS

The chief contraindication to the intravenous administration of calcium salts is the presence in the body of drugs of the digitalis group. Digitalis and calcium exert an additive effect on the heart, as shown by Bower and Mengle and by Lieberman,[25] so that there is danger of the production of ventricular standstill if the two drugs are used concomitantly. Theoretically, a value for blood sugar which is already low may be further lowered to a point at which hypoglycemic symptoms will be produced in the patient. Glucose administered intravenously would in such circumstances counteract the production of these symptoms, so that the possible production of hypoglycemia is not to be considered a contraindication to the administration of calcium if the value for blood sugar is carefully maintained at normal by means of the administration of glucose. Consideration of the effects of the administration of analgesic agents to women in labor who are receiving calcium will be found in the next section of this paper.

COMMENT

It seems probable that stimulation of the uterus by the administration of calcium may be employed to good advantage clinically in cases of uterine inertia. Utilization of the effects of calcium was unsuccessful when the patient was not definitely in labor. This conclusion is in accord with Reynolds' observation that calcium does not stimulate the uterine fistula of rabbits unless the fistula has been contracting rhythmically beforehand. The pains that follow administration of the oxytocic principle of the posterior lobe of the hypophysis (pitocin) and castor oil are not to be construed as being true labor pains, unless the uterine cervix dilates and thus indicates that the pains are valid labor pains. Duration of the effect of calcium appears to be two to three hours. If the calcium has not accomplished its purpose within this time, there seems to be no reason why it should not be administered again, although this was not done in our series. Even though calcium does increase the frequency and intensity of uterine contractions, it cannot be expected to overcome the dystocia which is produced by pelvic disproportion or by improper position of the presenting part, and the fact that it does not overcome such a type of dystocia would be an advantage rather than an objection to the administration of calcium. The obstetrician need not fear that rupture of the uterus in such cases would result from overstimulation by calcium. The ideal case in which to use calcium would be one in which labor has been definitely established, in which uterine contractions are weak to moderate and occur less often than every three minutes, and in which there is no obstruction present to hinder passage of the presenting part. Dilatation of the cervix is of no moment. In such a case it could be reasonably expected that the administration of calcium would increase the frequency and intensity of uterine contractions so that labor would be terminated sooner than would be the case if calcium had not been employed. In case calcium should be used therapeutically, hard, frequent uterine contractions would render its administration unnecessary, but in our study no harm re-

sulted from its use in such instances. Comparatively small doses of analgesic agents in the form of pentobarbital sodium or elixir of paraldehyde were administered orally to some of these patients according to the usual indications for such agents, although care was exercised not to employ the drugs until after the effect of the calcium had been established.* Five patients received no analgesic agent. Two additional patients received no analgesic agent until twenty-four to forty-eight hours had elapsed after administration of calcium. Eight patients received pentobarbital sodium before calcium was administered. Dosage for these patients varied from 1½ gr. (0.1 Gm.) administered two minutes before injection of calcium to 6 gr. (0.4 Gm.) administered two to four hours before injection of calcium. Sixteen patients received analgesic agents after the administration of calcium. Among these were 5 patients who had received some type of analgesic agent previous to the injection of calcium. Of the 16 patients previously mentioned, 13 received analgesic agents from fifteen minutes to three hours after the injection of calcium. Pentobarbital sodium in doses of 1½ to 6 gr. (0.1 to 0.4 Gm.) and 4 drachms each of paraldehyde and aromatic elixir, making a combined dose of 8 drachms (31.0 Gm.), were employed separately. In 2 cases administration of these agents was combined so that 3 gr. (0.2 Gm.) of pentobarbital sodium and 8 drachms (31.0 Gm.) of elixir of paraldehyde were administered. That uterine contractions which have been stimulated by the administration of calcium may slow or even cease when analgesic agents are administered soon afterward was noted in 2 of the 16 cases. It would seem prudent, therefore, to withhold analgesic agents from calcium-treated patients who have uterine inertia until definite progress has been made. If analgesic agents are administered, they must be used with the knowledge that they may defeat the purpose of the calcium.

SUMMARY AND CONCLUSIONS

A series of 26 patients in labor received solutions of calcium gluconate intravenously. After the injection of calcium gluconate the blood pressure increased slightly and the pulse rate decreased slightly, on the average. The respiratory rate was relatively unchanged. Regurgitation of gastric contents occurred in 19 per cent of cases, but it was not a troublesome feature.

On the basis of our observations it may be concluded that:

1. The administration of calcium will not relieve labor pains.
2. The administration of calcium will increase the intensity of uterine contractions and will decrease the interval between contractions but will not increase the duration of contractions. It is most useful in stimulation of the uterus in cases of inertia in the first or second stage of labor, but it cannot be expected to overcome severe dystocia.
3. The administration of analgesic agents, such as pentobarbital sodium and paraldehyde, may defeat the purpose of calcium in some cases of uterine inertia.

*The effects of the administration of analgesic agents do not appear in Tables I, II, or III.

4. The administration of calcium apparently has no ill effects on newborn babies whose mothers received calcium intravenously during labor.

5. On the basis of reports in the literature, it would appear that calcium should not be administered if a drug of the digitalis group already has been administered.

6. The authors hope that the results of this investigation will stimulate additional study of the effects of the therapeutic administration of calcium during labor, so that further evaluation of the procedure as a therapeutic measure can be made.

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THE USE OF SYNTHETIC VITAMIN E IN THE TREATMENT OF ABORTION

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INCREASING attention is steadily being focused upon the treatment of threatened and habitual abortion. This display of interest is justly warranted when one considers the importance of an uninterrupted pregnancy to the expectant mother and especially from a broader standpoint to the country, in the face of a national decreasing birth rate.

The statistical figures on abortions in general are very difficult to analyze; difficult because patients are wont to give inaccurate records, especially when criminal intent is suspected. Some observers report the incidence of abortion in pregnancy, ranging from 1 in 5[1] to 1 in 2.3.[2] However, among women of a fairly intelligent class, where a large majority want babies, Galloway and Paul[3] report that abortion, both early and late occurred in about 8 per cent of their cases. In addition, Bishop,[4] in a study of 7,008 pregnancies, reports 385, or 5.2 per cent, terminating in abortion. In this same series, 10.8 per cent of the women aborted at some time in their obstetric history. A recent survey, by American authors, shows that there are about 240,000 noninduced abortions in the United States each year.[5] These figures represent a challenge to the obstetrician, which should be met with all the possible resources at his command. With these facts in mind, both the clinician and the laboratory investigator have been engaged in the search for additional information relating to the physiology, pathology, and biomechanism of spontaneous abortion. An interesting report by Huntington[6] demonstrates that 70 per cent of the fetuses are dead or abnormal when the threatening begins. In view of such figures, the valuation of the merit of any form of therapy in the prevention of abortion is difficult. As for the causes of spontaneous miscarriages, Rock[7] states that most spontaneous miscarriages are caused by intrinsic disturbances in the fertilized ovum, or in the maternal organism, and not by the traditional extrinsic environmental accidents to the mother. In addition, he believes that sterility and miscarriage have, in large part, a common causative factor and merely represent different degrees of diminished fertility.

The treatment of threatened and habitual abortion has passed through a series of major phases. These are, on the basis of a broad classification, complete bed rest, sedatives, endocrine therapy, and finally, vitamin therapy. Complete bed rest has not been discarded entirely as a method of treatment, for it is still being used in conjunction with the more recently advocated measures. Sedation is still being employed but primarily as an adjunct to endocrine and/or vitamin therapy. Morphine, which was formerly the most widely used sedative for this purpose, is gradually being replaced by the barbiturates. This change has come about since Dodek,[8] and Falls, Lackner, and Krohn[9] have demonstrated that morphine not only fails markedly to inhibit uterine contractions, but may tend to stimulate them. In addition, we are all acquainted with the relative hastening dilatation of the cervix, which frequently takes place during the first stage of labor when morphine is used, suggesting a definite stimulating effect on the uterus.

The use of endocrines in the treatment of threatened and habitual abortion has come to the fore with increasing knowledge of the control of uterine motility.

Reynolds and Allen,[10] Allen and Reynolds,[11] and Krohn, Falls, and Lackner,[9] and others have demonstrated the inhibitory effect of the corpus luteum hormone, progesterone, on uterine motility. It is upon this physiologic fact that this form of therapy is based. Satisfactory reports, substantiating the effectiveness of this plan of treatment, have appeared in the literature. Thus, Bishop,[4] Gershenfeld,[12] Falls, Lackner, and Krohn,[13] and Campbell and Sevringhaus[14] have successfully used progesterone. The results of the latter two investigators were not very encouraging when used for threatened abortion. In addition, Rosenfeld[15] has obtained good results by using the blood serum of pregnant women. The effective agent involved in his treatment was probably the gonadotropic hormone, which is known to be present in abundance during pregnancy. Thyroid extract has also been employed with equal success for the prevention of abortion by King and Herring.[16] Kane[17] has reported the combined usage of thyroid and progesterone to be effective in repeated spontaneous abortions. Two groups of investigators, Johnstone, Wiesner, and Marshall,[18] and Finkler,[19] have reported the successful employment of anterior pituitary-like sex hormone in the treatment of both threatened and habitual abortion.

Recently, however, vitamin E has been more widely employed, both as an adjunct to, or in place of, the endocrines as a therapeutic agent for these conditions.

Observations supporting the value of vitamin E in the prevention of abortion are to be found in the reports of Vogt-Möller,[20] Currie,[21] Shute,[22] Watson and Tew,[23] Watson,[24] and Collins, Weed, and Collins.[25]

We, therefore, can see the relative merits of the various aforementioned means of treating threatened and habitual abortion. The different methods are worthy of application, either individually or combined. Practitioners may elect one or a group of methods which have been proved to be reasonably effective. The authors have utilized several of the foregoing agents with satisfactory results. In addition, more recently we have employed alpha-tocopherol acetate in the treatment of threatened, previous, and habitual abortion. The results of these experiences form the basis of this report.

CHEMISTRY AND PHYSIOLOGIC ACTION

Evans and Bishop,[26] in the course of their studies on fertility in rats, found an antisterility factor, which was called "X" and later became known as vitamin E. This factor was fat soluble and insoluble in water (Evans and Burr[27]) and concentrates could be prepared from fairly fresh wheat germ oil, whose potency could be maintained for a period of years when kept vacuum sealed.[28] Emerson and others,[29] found that alpha-tocopherol was identical in vitamin E activity as the substance isolated from wheat germ oil, and the authors also isolated beta-tocopherol and gamma-tocopherol which they found to be only from one-half to one-fourth as active as alpha-tocopherol. In 1938, Karrer[30] and his associates described the synthesis of alpha-tocopherol and a graphic formula was published by Kunz[31] in 1938. Evans and Burr[27] suggest that "sterility is a dietary deficiency disease which leads to the destruction of the germ cell in the male while in the female the ovary and ovulation remained unimpaired but there is a characteristic disturbance in gestation with the death and resorption of the developing young." Rat experiments showed further that vitamin E, which was necessary for development of the fetus and completion of gestation, could not be replaced by either pituitary hormone or prolan A.[32] Rowlands and Singer[33] found that extracts of the pituitaries of rats

fed on a vitamin E deficient diet are less potent in inducing ovulation on injection into estrous rabbits than extracts made from pituitaries of normal control rabbits. In addition, it appears as if it is the luteinizing substance of the pituitary, and not the follicle-stimulating substance which is decreased or depressed by a vitamin E deficiency. To test for toxic effects,[34] large doses of vitamin E (alpha-tocopherol synthetic and its acetate) were given to mice, dogs, rats, and cats without any such effects being noted. Rowntree and co-workers[35] and Dorrance and Ciccone[36] fed albino rats on unrefined and crude wheat germ oil and were able to produce abdominal tumors, microscopically identified as sarcomas, which could be successfully transplanted, subcutaneously and intraperitoneally. However, further investigators, Carruthers,[37] Evans and Emerson,[38] and Halter,[39] could not produce sarcomas, using concentrated wheat germ oil preparations. In addition, Davidson,[40] by administering large doses of vitamin E, could inhibit, in many cases, the development of carcinoma in mice subjected to tarring, and therefore, believes in the anticarcinogenic value of wheat germ oil.

The clinical application of the above data has been reported by several observers whose findings will be briefly mentioned. Cromer[41] found that vitamin E, when given early, and in sufficient dosage, had some value in cases of recurrent and threatened abortion. Watson[24] reported good results in habitual, previous, and threatened abortions, but found wheat germ oil without any effect in his cases of sterility. Shute[42] found that there was a deficiency of vitamin E in his cases of spontaneous abortion, and he called attention to the value of wheat germ oil as a prophylactic and therapeutic treatment for such cases. His results were very satisfactory. Large doses of vitamin E were found to occasionally produce an idiosyncrasy in certain individuals.[43] In further experiments, he found no basis for apprehension that labor might go beyond term or never observed any delay in the onset of labor due to the oil.[44] Watson and Tew,[23] Currie,[21] and Vogt-Möller,[20] also report very enthusiastically on the usage of vitamin E for habitual abortion. More recently, Collins and co-workers[25] reported the efficacy of wheat germ oil along with thyroid and progestin in combating threatened and habitual abortion, and dispelled the fear of a delivery of a malformed fetus in those cases in which abortion had been successfully treated. Blood serum studies indicating deficiency of vitamin E could not be corroborated by this group in their cases, nor could Cuthbertson and Drummond[45] demonstrate an excess of antitryptic activity in the serum in vitamin E deficient rats.

PATIENTS STUDIED

The cases studied included only private patients. Service cases were not utilized for several distinct reasons. Private patients present a more accurate history pertaining to previous pregnancies and can be depended upon to carry out instructions and report symptoms more reliably. In addition, when a woman employs a private physician for delivery, she signifies her desire of bearing a child, whereas when clinic patients are admitted to general wards, there is no way of checking criminal induction of abortion. Moreover, service patients are not as willing to divulge this evidence as are private patients.

All of the patients observed, with one exception, were hospitalized,* either at the time of threatening to abort or when ready for delivery. The one exception was a woman who aborted at home during the eleventh week of pregnancy. Another patient threatened to abort while in the hospital, following an appendectomy during the fifth month of pregnancy.

The patients were divided into three groups, as follows: habitual abortion, including those who had two or more spontaneous abortions (there were 7 in this group); previous abortion, comprising those who

*At the Prospect Heights Hospital or the Swedish Hospital in Brooklyn.

had one previous spontaneous abortion (there were 10 in this group); threatened abortion, of which there were 15. This made up the largest group. Vaginal examination was omitted in all patients until after the period of viability was reached.

METHOD

All 7 of the patients who had habitual abortions, with one exception, received 3 mg. alpha-tocopherol acetate* daily, starting with their first prenatal visit. The stages of pregnancy at which therapy was begun ranged from four to eleven weeks. The duration of therapy was from forty-four to one hundred and ninety-six days. The period of pregnancy to which treatment was continued, extended from the twentieth to the thirty-fifth week. The minimal total dosage was 132 mg. and the maximal, 561 mg. The one exception (Case 1), mentioned above, was started with wheat germ oil, prior to the availability of alpha-tocopherol acetate, and the patient received a total of 420 c.c. of the oil, after which the treatment was continued with the acetate.

The plan of treatment for the "previous" abortion group was essentially similar to that of the "habitual" group. Each patient, with one exception, received 3 mg. of alpha-tocopherol acetate daily. The earliest treatment was begun at five weeks and the latest at twelve weeks and continued up to periods of pregnancy ranging between fourteen and thirty-six and one-half weeks. The minimal total dosage was 273 mg. over a period of ninety-one days, and the maximal, 570 mg. over a period of one hundred and ninety days. The one exception (Case 8), received 276 c.c. of wheat germ oil before initiating alpha-tocopherol acetate therapy. The initial dose of alpha-tocopherol acetate for "threatened" abortion varied between 3 mg. and 48 mg. administered orally in divided doses during the first twenty-four hours after symptoms began. Following this initial period, the dosage was usually maintained at 3 mg. daily unless symptoms persisted or re-appeared. Treatment continued for from two days to one hundred and one days, depending upon the severity, duration, and return of symptoms. Bleeding, with or without pain, was regarded as indicative of threatened abortion. One patient, postappendectomy, referred to above, had pain without bleeding. She had markedly severe pain, associated with intermittent uterine contractions of moderate force during the fifth month of pregnancy. With the two exceptions referred to above, alpha-tocopherol acetate by mouth, was the only therapeutic agent in "previous" and "habitual" abortion.

In the "threatened" type, however, bed rest was employed in addition when symptoms appeared, and was continued until all bleeding or pain had disappeared for at least four days. No other therapy was employed, except in one patient, where progesterone was used, parenterally, previous to, and immediately following appendectomy during the fifth month of pregnancy. This was used because of the inadvisability of oral medication preoperatively, and the inability to take oral medication postoperatively because of vomiting. This was only used as a preventive measure. When, however, the symptoms of threatened abortion appeared eight days postoperatively, and vomiting was no longer present, the alpha-tocopherol alone was employed.

Toxic manifestations were not associated with the use of alpha-tocopherol acetate in any of the patients under observation in this study, nor were any idiosyncrasies encountered.

RESULTS

In the "threatened" abortion group, there were 15 cases in all. Two patients (Cases 25 and 32) aborted, one at eleven weeks, after two days of therapy, and the other at fourteen weeks, after ten days of therapy. There was one stillbirth (Case 27), in which case, death of the fetus occurred during a long labor with inertia uteri, and the post-mortem examination of the fetus showed pulmonary atelectasis. The remaining 12 delivered normal full-term infants. There was one cesarean section in this group (Case 19) because of cephalopelvic disproportion. In calculating

*Ephynal-3 mg. tablets supplied through the courtesy of Hoffman-LaRoche, Inc.

TABLE I. HABITUAL ABORTIONS

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORT.	PREVIOUS THERAPY	THERAPY		TOTAL DOSAGE (MG.)	TOTAL TIME (DAYS)	E.D.C.‡	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
							BEGAN	ENDED							
1	S. S.	26	iii	0	(1) 14 wk. (2) 22 wk.	none WGO†	4 wk. 19 wk.	19 wk. 32 wk.	420 c.c. wheat germ oil 273 mg.	105 91	2/25/40	2/23/40	9 hr.	Live birth	Stained 1 day at 16 weeks
2	E. R.	28	vi	0	(1) Induced (2) Sp. ab.* (3) Sp. ab. 4½ mo. (4) Sp. ab. 5 mo. (5) Sp. ab. 7 mo.	none none none proges-tin WGO†	9 wk.	15 wk.	132	44	3/ 7/41	9/13/40		Aborted	Abortion at 15 weeks
3	B. S.	32	iv	i	(1) Sp. ab. 6½ mo. (2) Sp. ab. 2 mo. (3) Live birth	none none proges-tin	10 wk.	26 wk.	354	118	7/ 3/40	7/ 4/40	5 hr.	Live birth	Stained on several occasions

4	S. J.	31	iv	0	(1) Sp. ab., 7 wk. (2) Sp. ab., 7 wk. (3) Sp. ab., 7 wk.	none none none	8 wk.	35 wk.	561	187	6/27/40	5/31/40	7½ hr.	Live birth	Stained on two occasions
5	J. B.	37	v	i	(1) Live birth (2) Therapeutic abortion (3) Sp. ab., 12 wk. (4) Sp. ab., 10 wk.	 none none none	9 wk.	24 wk.	312	104				Aborted	Abortion at 20 weeks
6	R. G.	32	iv	i	(1) Live birth (2) Sp. ab., 8 wk. (3) Sp. ab., 11 wk.	 none none	11 wk.	35 wk.	483	161	7/29/40	8/ 3/40	24 hr.	Live birth	
7	R. Y.	35	iv	i	(1) Live birth (2) Sp. ab., 3½ mo. (3) Sp. ab., 7 mo.	 none none	8 wk.	32½ wk.	516	172	10/12/40	10/15/40	19 hr.	Live birth	

*Sp.Ab., Spontaneous abortion.
†WGO., Wheat germ oil.
‡E.D.C., Estimated date of confinement.

TABLE II. PREVIOUS ABORTION

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORTIONS	THERAPY		TOTAL DOSAGE (MG.)	TOTAL TIME (DAYS)	E. D. C.‡	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
						BEGAN	ENDED							
8	R. S.	24	ii	0	Sp. Ab.* 11 wk.	5 WGO† 15	15 wk. 28 wk.	273	91	3/ 7/40	3/ 3/40	37 hr.	Live birth	
9	J. O.	34	ii	0	Sp. Ab. 12 wk.	9	36½ wk.	267	189	4/24/40	4/15/40	12 hr.	Live birth	
10	M. T.	29	ii	0	Sp. Ab. 9 wk.	7	26 wk.	333	111	7/ 5/40	5/19/40	4 hr.	Live birth, lived 24 hr.	Intestinal obstruction in mother. Progestin pre- and postoperative
11	J. S.	27	ii	0	Sp. Ab. 11 wk. Proluton therapy	6	34 wk.	570	190	7/10/40	7/15/40	6 hr.	Live birth	
12	M. W.	36	iii	i	Live birth Sp. Ab. 10 wk.	5	14 wk.	300	98	7/30/40	7/27/40	2 hr.	Live birth	Stained on 2 occasions. Placenta showed partial separation
13	E. L.	36	iii	i	Live birth Sp. Ab. 12 wk.	5	18 wk.	285	95	8/ 5/40	7/28/40	3½ hr.	Live birth	
14	I. G.	30	ii	0	Sp. Ab. 10 wk.	8	27 wk.	399	133	9/11/40	7/22/40	no labor	Live premature	Cesarean section for advancing toxemia. Stained once during pregnancy
15	R. R.	28	ii	0	Sp. Ab. 12 wk.	8	32 wk.	432	164	10/ 5/40	10/ 8/40	2½ hr.	Live birth	
16	F. H.	25	iii	0	Induced Ab. 6 wk. Sp. Ab. 8 wk.	12	33 wk.	414	138	10/17/40	10/21/40	3 hr.	Still-birth	Toxemia of pregnancy. Infant died two days before labor
17	M. T.	29	ii	0	Sp. Ab. 11 wk.	6	31 wk.	528	176	12/28/40	1/ 2/41	10½ hr.	Live birth	

*Sp.Ab., Spontaneous abortion. †WGO, Wheat germ oil. ‡E.D.C., Estimated date of confinement.

TABLE III. THREATENED ABORTION

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORTION	SYMPTOMS		TIME OF ONSET	TOTAL DOSAGE	TOTAL TIME	E. D. C.*	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
						PAIN	BLEEDING								
18	Y. G.	31	i	0	0	No	Yes	10 wk.	150 mg.	50 days	3/26/40	4/ 9/40	8 hr.	Live birth	
19	D. C.	34	ii	i	Stillbirth	Yes	No	22 wk.	150 mg.	50 days	12/19/40	12/17/40	11 hr.	Live birth	Cesarean section, syphilitic, cardiac, cephalopelvic disproportion
20	S. M.	32	ii	i	0	Yes	Yes	9 wk.	303 mg.	101 days	4/16/40	3/31/40	4½ hr.	Live birth	
21	I. A.	34	i	0	0	No	Yes	11 wk.	225 mg.	67 days	4/ 6/40	4/10/40	15 hr.	Live birth	
22	J. J.	26	i	0	0	Yes	No	21 wk.	84 mg.	7 days	4/12/40	4/10/40	9 hr.	Live birth	Appendectomy at 20 weeks. 1 wk. postoperative painful contractions
23	L. R.	28	i	0	0	No	Yes	11 wk.	42 mg.	7 days	7/ 8/40	7/ 9/40	1¾ hr.	Live birth	Cardiac mother
24	A. D.	33	i	0	0	No	Yes	7 wk.	200 mg.	68 days	8/ 7/40	7/27/40	3 hr.	Live birth	
25	S. B.	26	i	0	0	Yes	Yes	11 wk.	9 mg.	2 days				Aborted	One year sterility
26	F. S.	34	iii	ii	0	Yes	Yes	21 wk.	27 mg.	7 days	5/19/40	6/16/40	4 hr.	Live birth	
27	R. E.	28	i	0	0	No	Yes	17 wk.	150 mg.	28 days	7/23/40	8/ 4/40	33 hr.	Stillbirth	Inertia uteri. Pulmonary atelectasis in infant
28	S. B.	29	i	0	0	No	Yes	9 wk.	159 mg.	52 days	10/24/40	10/18/40	18 hr.	Live birth	
29	S. S.	27	ii	i	0	Yes	Yes	18 wk.	150 mg.	49 days	8/30/40	8/30/40	6 hr.	Live birth	
30	B. K.	32	ii	i	0	Yes	Yes	19 wk.	135 mg.	41 days	8/31/40	9/ 6/40	12 hr.	Live birth	
31	P. T.	32	i	0	0	No	Yes	11 wk.	129 mg.	42 days	11/19/40	11/17/40	6½ hr.	Live birth	
32	B. H.	34	i	0	0	Yes	Yes	14 wk.	39 mg.	10 days				Aborted	

*E.D.C., Estimated date of confinement.

our statistics, we found that the drug failed to arrest the threatened abortion in two cases, while one patient delivered a stillbirth. The percentage of success is therefore 80.

Of the 7 cases of habitual abortion, 5 patients delivered normal full-term infants. There were 2 failures (Cases 2 and 5), in which cases the abortion occurred at the fifteenth and twentieth weeks, respectively. With 2 failures in this group, the percentage of success is 71.5.

Eight of our 10 patients with previous abortions delivered live infants. One failure (Case 10) was one complicated by intestinal obstruction in the mother. Thirty-six hours postoperatively, the patient delivered a thirty-four-week fetus, which died after twenty-four hours. The second failure (Case 16) was that of a late toxemia of pregnancy, in which case the infant died two days before labor began. The patient in Case 14 had a cesarean section for a progressive toxemia of pregnancy, and a live, premature infant, which survived, was delivered. In this group, the percentage of success was 80. The two deaths in the infants resulted from accidents or complications of the last trimester of pregnancy and were not related to the factors causing abortion.

DISCUSSION

The authors fully appreciate the difficulty in evaluating the therapeutic importance of any method or agent to prevent spontaneous abortion. It is recognized that spontaneous abortion, not uncommonly, threatens pregnancies, where the latter continue successfully to term without any measures having been taken to combat possible accident. It is also conceded that many habitual and previous aborters, may, without aid, carry subsequent pregnancies to successful termination. Unfortunately, reports citing accurate figures of these instances are not commonly available. However, a very recent report[5] tends to show that after one spontaneous abortion, the expectancy that the next pregnancy will not result in an abortion is about 70 per cent; and that after 2 abortions the expectancy of no abortion in the next pregnancy is about 30 per cent. From reports of numerous observers, however, the various therapeutic agents, cited earlier in this report, appear to offer a more satisfactory opportunity for a full-term pregnancy, than is available without therapy to the type of patient under observation. Although one must be cautious in ascribing a fruitful pregnancy to any specific therapeutic measure, yet one cannot completely disregard the value of those agents, which appear to help. Thus, the various sedatives, hormones, and vitamins have earned their place in the treatment of threatened and habitual abortion. It is with a similar thought in mind that these studies were undertaken, toward the possible inclusion of an additional measure in the armamentarium of the obstetrician to combat spontaneous abortion. That this is worth while, can be attested to by the happiness of those mothers who have apparently been benefited by such efforts. The fear of abnormal babies resulting from pregnancies of successfully treated threatened abortions, is probably unfounded. Falls, Lackner, and Krohn,[9] encountered none in their series, nor did Collins and his co-workers[25] referred to above. The former group, however, reported 2 abnormal fetuses in 2 of the failures that aborted. The large number of normal infants born after therapy was instituted, during their threatening attempts, are difficult to correlate with the number of abnormal fetuses reported by Huntington and referred to above. To look further perhaps into the negative side of the question, as to the

effectiveness of certain therapeutic biologic agents, we cite a few observations. Galloway and Paul[3] observed 2 cases of threatened abortion where proluton led to a prompt increase in pain and bleeding followed by rapid abortion. Sevringhaus and Campbell[14] report relatively little success in the treatment of threatened abortion with progestin. Young[46] further questions the effectiveness of small doses of prolan when the excretion of the hormone in a normal pregnancy reaches many thousand times the quantity employed. Caution is necessary in evaluating the effectiveness of the apparently small doses of progesterone employed with evident success. The doses theoretically are insufficient when compared with the normal excretion rate of pregnanediol cited by Venning and co-workers.[47] Dietetic influences affect the reproductive process, and lack of vitamins A and E are attended by serious interference with the intrauterine development of the fetus. The varied biologic and vitamin preparations all seem to be successful in a relatively large number of cases, and we hope that future laboratory workers will help correlate the mechanisms by which these therapeutic agents act.

SUMMARY

1. Evaluation of various prophylactic and therapeutic agents in the treatment of abortion is presented.

2. Alpha-tocopherol acetate, a synthetic vitamin E oral preparation, was used in the treatment of threatened, previous, and habitual abortion in a total of 32 cases.

3. In this series there were 15 threatened, 7 habitual, and 10 previous abortions.

4. In the threatened abortion group, 80 per cent of the patients delivered normal infants. In the previous abortion group, the percentage of success was 80, while in the habitual abortion group, the percentage of success was 71.5.

5. No abnormalities of the fetus have been observed.

CONCLUSION

Caution is necessary in evaluating the effectiveness of synthetic vitamin E in the treatment of threatened, previous, and habitual abortion. We realize that our report is based on the study of a group of cases too small in number to warrant a positive conclusion. However, we do feel that the results are sufficiently encouraging to stimulate further investigation by others.

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ON THE MAGNESIUM SULFATE AND ETHER CIRCULATION TIMES DURING PREGNANCY*

A Study of 300 Patients

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THE last few years have witnessed great strides in the study of the physiologic changes taking place in the maternal circulation during pregnancy. One of the phases concerning which there is very little consonance of opinion is the changes in the circulation time (the inverse variant of the blood velocity). Our attention was attracted some time ago by the marked increase in blood velocity observed in a small group of pregnant women.[1, 2] In the present study our investigation was furthered in an extensive group of pregnant women.

In 1880 Remy[3] claimed that the blood velocity was increased during pregnancy. To explain the functional murmurs of pregnancy Fromme[4] used Sahli's explanation[5] that functional murmurs are caused by increased blood velocity. Kautsky[6] postulated that the blood velocity is increased in pregnancy. Klee,[7] in 1924, using the fluorescein method of Koch,[8] found the average circulation time in pregnancy within the upper normal limits of that method (thirteen to twenty-five seconds).

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In 1933 Spitzer,[9] using the decholin method[10-12] in 27 normal pregnant women, found the blood velocity within the normal limits of that method (ten to sixteen seconds, average 14.3 seconds). There was some slowing of the circulation in 4 cases of toxemia of pregnancy, in 3 cases of eclampsia, and in 1 case of mitral stenosis. In 1936 Cohen and Thomson[13] employed the cyanide method of Robb and Weiss[14] in 36 normal pregnant women. There was a decrease in the average arm-to-carotid circulation time from the seventeenth to the thirty-sixth week of pregnancy inclusive; an increase in the average circulation time (relative to the seventeenth to thirty-sixth week period) from the thirty-seventh to the fortieth week reaching a peak value at the thirty-eighth week of 15.6 seconds (which is the average value in normal nonpregnant women); and a decrease in the average circulation time following delivery which persisted until the seventh post-partum week. In 1937 Greenstein and Clahr[15] published the results of 52 saccharin arm-to-tongue determinations[16] in 13 normal pregnant women. Their average value varied from 10.9 seconds at the eighteenth week of gestation to 14.7 seconds at the thirty-eighth week, followed by a decrease to 13.5 seconds at the time of delivery. This progressive delay was exhibited by 10 of the 13 cases, and then only in irregular fashion.

MATERIAL

The present series comprised 300 pregnant women between the ages of 17 and 40 years. One hundred and twelve were primiparas; 188 ranged in parity from secundiparity to undeciparity. The average age of the primiparas was 23.0 years and of the multiparas 28.8 years. Both magnesium sulfate and ether circulation times were performed successively, the tests being repeated monthly on each patient when circumstances permitted; one and preferably two determinations of both circulation times were determined during the two weeks after delivery. The number of observations on the same patient varied between one and five. Special attention was paid to the week prior to delivery and the two weeks post partum.

A total of 599 magnesium sulfate and 546 ether circulation times were determined: 564 magnesium sulfate circulation times were performed on 285 normal pregnant patients, and 511 ether circulation times in 274 patients of this group; 15 magnesium sulfate and 15 ether circulation times in 6 patients with rheumatic heart disease; and 20 magnesium sulfate and 20 ether circulation times in 9 patients with toxemias of pregnancy. The duration of gestation was calculated back from the actual day of delivery, the duration of a full-term pregnancy being taken as ten lunar months or two hundred and eighty days.

TECHNIQUE

The patient reclines as nearly as possible flat in bed with the arm held at the level of the right auricle. She is informed that she will experience the sudden onset of a transient hot sensation in the pharynx and tongue which she is instructed to signal with the word "now." She is also cautioned to relax as much as possible. Five cubic[1, 2] centimeters of a warm 10 per cent aqueous solution of magnesium sulfate,* drawn up in a 10 c.c. syringe with an 18 gauge needle, are injected as rapidly as possible in a large antecubital vein. The circulation time is recorded with a stop watch from the beginning of the injection until the onset of the end point. To facilitate the test and insure accuracy when it is performed by one person unassisted, it has been our practice to start the stop watch and to begin the injection at the moment the hand of the stop watch is crossing the

*Magnesium sulfate (reagent crystals), Merck and Company, Inc., was used in this investigation.

five second mark. The five seconds are subtracted from the circulation time that is finally recorded. The test may be repeated within a few minutes with practically duplicate results. The safety of the test has been amply demonstrated.[1, 17] The magnesium sulfate circulation time (arm-to-tongue time) serves as an index of the functional capacity of the heart as a whole.

With the needle in situ, and after the lapse of about one minute, the ether circulation time is then determined.[18, 19] A mixture of 5 minims of ether and 5 minims of warm normal saline previously drawn up in a tuberculin syringe are injected as rapidly as possible. The time is recorded from the moment of injection until the onset of the end-point which is the perception of ether by the patient or by the observer. Usually this is accompanied by a cough or grimace on the part of the patient. The ether test thus has the advantage of being both subjective and objective. The ether circulation time (arm-to-lung time) serves as an index of the functional capacity of the right side of the heart. The magnesium sulfate circulation time reading minus the ether circulation time reading is equivalent to the lung-to-tongue circulation time and serves as an index of the functional capacity of the left side of the heart.

RESULTS IN NORMAL PREGNANCY

1. *Magnesium Sulfate (Arm-to-Tongue) Circulation Time.*—Five hundred sixty-four determinations of the magnesium sulfate circulation time were performed in 285 normal pregnant women; 312 observations ante partum and 252 post partum (Table I). The arm-to-tongue circulation time ante partum varied between 5.5 seconds and 15.2 seconds, an average of 9.9 seconds; post partum between 6.8 seconds and 15.2 seconds, an average of 10.4 seconds. These figures may be contrasted with the range in normal nonpregnant women of 7.0 to 17.8 seconds, an average of 12.9 seconds.[1]

TABLE I. MAGNESIUM SULFATE CIRCULATION TIMES IN NORMAL PREGNANCY

	PRIMIPARAS		MULTIPARAS		ENTIRE SERIES		TOTAL
	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	
No. of tests	117	93	195	159	312	252	564
Average value (Sec.)	9.5	9.7	10.1	10.7	9.9	10.4	
Range (Sec.)	5.5–15.0	6.8–12.6	7.0–15.2	7.4–15.2	5.5–15.2	6.8–15.2	
No. of patients	105		180				285

During the first four months of gestation, the arm-to-tongue circulation time shows a tendency to diminish gradually (Fig. 1, *A*). It should be noted, however, that even in this uncertain period the circulation time shows a definite trend to fall below the average nonpregnant value. From the sixteenth week through the thirty-fifth week of gestation, there seems to be a definite decrease in the average arm-to-tongue circulation time, the level being fairly well maintained between 9.0 and 10.0 seconds. In the latter portion of this period (twenty-ninth to thirty-fifth week inclusive), there is a steady slope from 10.0 seconds to 9.4 seconds. In the thirty-fifth to fortieth week there begins a steady though very moderate increase in the arm-to-tongue circulation time, ranging from 9.4 seconds to 11.0 seconds. During the week preceding delivery, this higher level is maintained fairly constantly. During the first 14 post-partum days, the level of the last ante-partum week is very little changed.

So far as a comparison of primiparas (105 patients) and multiparas (180 patients) is concerned, no definite conclusion may be drawn, although the tendency of multiparas to maintain a relatively more even trend of circulation time than do primiparas must be noted. Moreover, the blood velocity is significantly more rapid in primiparas than in multiparas, both ante partum (9.5 seconds and a range of 5.5 to 15.0 seconds as compared with 10.1 seconds and a range of 7.0 to 15.2 seconds) and post partum (9.7 seconds and a range of 6.8 to 12.6 seconds as compared with 10.7 seconds and a range of 7.4 to 15.2 seconds) (Table I).

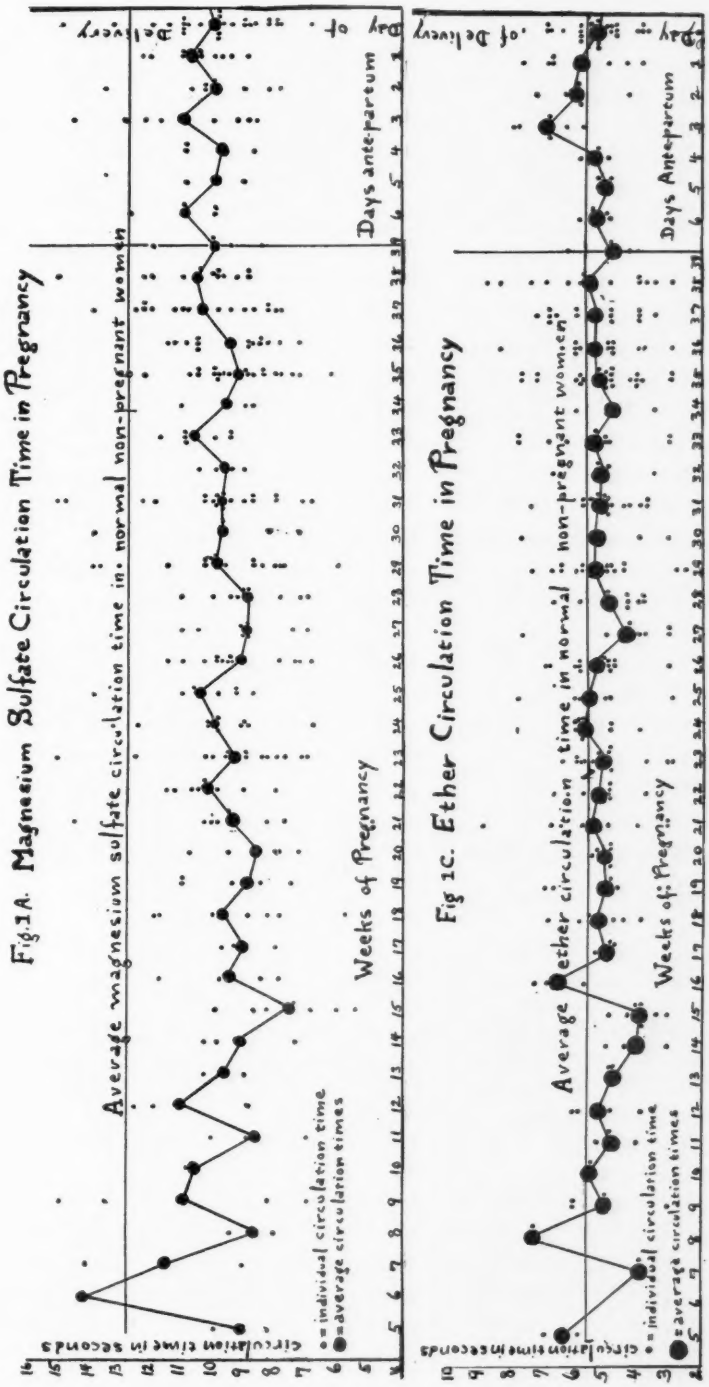
Fig. 1A. Magnesium Sulfate Circulation Time in Pregnancy
Average magnesium sulfate circulation time in normal non-pregnant women
Circulation time in seconds
o = individual circulation time
● = average circulation times
Weeks of Pregnancy
Days ante-partum
Day of Delivery
Fig 1C. Ether Circulation Time in Pregnancy
Average ether circulation time in normal non-pregnant women
Circulation time in seconds
o = individual circulation time
● = average circulation times
Weeks of Pregnancy
Days Ante-partum
Day of Delivery

Fig. 1.

II. Ether (Arm-to-Lung) Circulation Time.—Five hundred eleven determinations of the ether circulation time were performed on 274 normal pregnant women, 290 observations being ante partum and 221 post partum (Table II). The arm-to-lung circulation time ante partum varied between 3.0 and 9.2 seconds, an average of 5.4 seconds; post partum, between 3.2 and 8.4 seconds, an average of 5.5 seconds. The ether circulation time in normal nonpregnant women averages 5.7 seconds, with extremes of 2.6 to 10.0 seconds.[1] The ante-partum and post-partum values agree quite closely. During the first four months of pregnancy, the changes in ether circulation time follow very closely the fluctuations in the magnesium circulation time. Therefore, Fig. 1, *C* demonstrates very clearly the striking uniformity of the ether circulation time during the entire course of pregnancy.

So far as a comparison of primiparas (101 patients) and multiparas (173 patients) is concerned, again the relatively faster blood velocity of primiparas must be noted, though the differences ante partum are negligible, and post partum slightly more striking.

III. Magnesium Sulfate and Ether Circulation Times in Toxemias of Pregnancy.—In a group of 9 patients with toxemias of pregnancy, 20 magnesium sulfate circulation times were determined, 16 ante partum and 4 post partum (Fig. 2). The

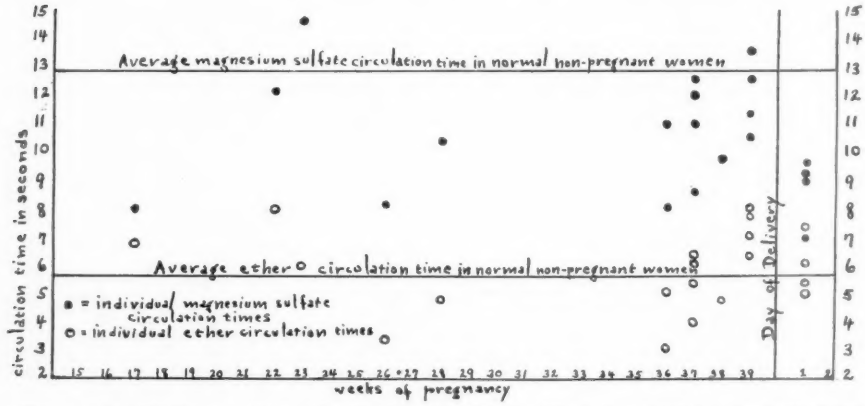

Fig. 2.—Magnesium sulfate and ether circulation times in toxemias of pregnancy.

patients were all in pre-eclamptic states with blood pressures ranging from 158 to 200 systolic and 96 to 148 diastolic. Two were primiparas and 7 multiparas, ranging in age from 19 to 39.

Practically all tests were done in the last four weeks of pregnancy. The average circulation time recorded ante partum was 10.9 seconds with extremes of 8.0 seconds and 13.6 seconds. Only 2 of the 20 readings were higher than the average value in normal nonpregnant women. The average circulation time post partum was 8.7 seconds with extremes of 7.0 seconds and 9.6 seconds.

TABLE II. ETHER CIRCULATION TIMES IN NORMAL PREGNANCY

	PRIMIPARAS		MULTIPARAS		ENTIRE SERIES		TOTAL
	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	
No. of tests	115	85	173	136	290	221	511
Average value (Sec.)	5.2	5.2	5.4	6.1	5.4	5.5	
Range (Sec.)	3.0–9.0	3.2–8.4	3.0–9.2	3.6–8.4	3.0–9.2	3.2–8.4	
No. of patients	101		173				274

Sixteen ante-partum ether circulation times averaged 5.9 seconds, with extremes of 3.2 seconds and 7.8 seconds; post partum 4 circulation times averaged 6.0 seconds, with extremes of 5.0 seconds and 7.4 seconds.

IV. Magnesium Sulfate and Ether Circulation Times in Rheumatic Heart Disease.—A small group comprised 6 patients with rheumatic heart disease, ranging in age from 21 to 26 years. Five were primiparas and one a multipara. Of the primiparas, one had mitral stenosis and syphilis, 3 had mitral stenosis and regurgitation, 1 had mitral regurgitation; the multipara had mitral stenosis and regurgitation. Five patients (including the multipara) were well compensated clinically. In this group, 10 ante-partum magnesium sulfate circulation times (practically all late in pregnancy) averaged 10.8 seconds (8.0 seconds to 13.6 seconds); 4 post-partum circulation times were each 9.6 seconds. Ten corresponding ante-partum ether circulation times averaged 5.4 seconds (4.2 seconds to 7.6 seconds); 4 post-partum determinations averaged 6.7 seconds (6.6 seconds to 7.4 seconds). The sixth patient (a primipara with mitral stenosis and regurgitation who had moderate dyspnea) had a magnesium sulfate circulation time of 14.0 seconds and an ether circulation time of 9.6 seconds nine days before delivery.

ETHER REACTIONS

When Hitzig published his work on the use of ether as a circulation time agent, in 1934,[37] he called attention to certain ether reactions: he encountered no untoward constitutional reactions; the subject usually was aware of a "creeping" feeling along the course of the vein; 25 per cent had transient pain in this location; and 3 thromboses were noted in 28 carefully followed patients. Curiously enough, reports of ether work subsequent to Hitzig's report fail to emphasize or mention such reactions. In our series numerous reactions were encountered: 24 cases presented pain of varying intensity and duration at the site of injection; 19 had intense pain in the shoulder, 8 had pain following the course of the vein and thence, high substernally; 4 had pain along the course of the vein; 1 had pain up the arm and into the angle of the jaw; 3 had pain radiating into the axilla; 1 had almost persistent vomiting for three days; 2 had pain in the shoulder accompanied by nausea; 4 nausea; and only 2 a "creeping" feeling along the course of the vein. No thromboses were encountered. One patient developed severe pain at the site of injection for a few seconds with radiation into the shoulder and a few inches below the elbow; fifteen minutes later the hand and arm became definitely colder than the corresponding limb. This sensation lasted only a few minutes. In several patients, pain, when it developed, was of such severity as to be almost shocking. In summation, 59 reactions developed in a series of 546 ether tests, an incidence of 10.8 per cent.

DISCUSSION

The circulation time values shown through the major portion of gestation and the immediate post-partum period indicate a marked speeding of blood velocity. This marked increase is further supported by other factors. An increase in cardiac output is usually demonstrable by the third or fourth month,[20-23] with the maximum cardiac output appearing from the sixth through the ninth lunar months. During the last four weeks of gestation (at a period when the circulation time begins to rise), the cardiac output falls[23, 24] toward normal though not to the average nonpregnant level, and after delivery it continues its fall toward the normal level.[20, 21, 26] Other factors remaining equal, the speed of the circulation varies directly with the cardiac output.[25] The changes in circulation time are, therefore, clearly linked with the changes in cardiac output.

Further corroboration of the circulation time changes is afforded by simultaneous studies of the cardiac output and oxygen consumption[22, 23]

which show a tremendous increase of cardiac output far out of proportion to the rise in oxygen consumption. Such a disproportionate increase implies a diminution in the arteriovenous difference or oxygen utilization and a speeding of the circulation.

"The viscosity of the blood is decreased in pregnancy up to the sixth month, is slightly increased in the seventh month, is unknown in the latter months, and presents a consistent post-partum rise."[13, 27] There is a steady increase from about the thirty-fifth week continuing through the post-partum period. Inasmuch as the velocity of a liquid varies inversely with its viscosity, the changes in blood viscosity may play an important role in the changes in circulation time. The analogy between blood velocity and blood viscosity, however, does not fit in with the changes in circulation time observed post partum. It must be kept in mind, however, that lactation may introduce physiologic changes that overshadow the seeming discrepancy between the blood velocity and blood viscosity changes during the puerperium.

Most studies [28, 29] of total blood volume changes during pregnancy indicate an increase of 42 per cent[30] to 65 per cent[31] closely paralleling the ante-partum changes in cardiac output. The fall in total blood volume during the last weeks of pregnancy may be an important factor in the diminution of cardiac output during that period. Moreover, as Cohen and Thomson[31] point out, a profound disturbance in blood volume is found in endocrine conditions,[28, 32] such as exophthalmic goiter. A possible linkage of the increase in blood volume and endocrine control is further indicated by a rather striking resemblance of the plasma volume trend with that of excretion of gonadotropic substance in normal pregnancy.[33] During pregnancy the thyroid increases in size, and there is a great deal of evidence[34, 35] that hyperfunction of the thyroid gland may be an important factor contributing to an increase in cardiac work during pregnancy. If this be the case, the rapidity of the blood flow in pregnancy may be at least partially explained on this basis, since hyperthyroidism is the prime condition in which the blood velocity is markedly accelerated.[36]

So far as the ether circulation time curve is concerned, the most striking feature is its similarity with the magnesium sulfate curve during the first few weeks of pregnancy. Thereafter, the ether time remains remarkably constant well into the puerperium. The implication is that during the aforementioned first trimester of pregnancy both the left and right sides of the heart share equally in the changes in the circulation; whereas from that point on, the right side of the heart remains relatively unaffected, and the left side of the heart takes the brunt of the "burden of pregnancy."

Careful study of our results demonstrates a somewhat close similarity with those obtained by Cohen and Thomson.[13] The chief differences are: first, a much faster absolute level of the blood velocity (which is undoubtedly due to the fact that with magnesium sulfate as a circulation time agent values obtained in all sorts of normal and pathologic conditions are always faster than those obtained with the use of sodium cyanide); and second, at the thirty-eighth week of gestation their circulation time values attained the normal nonpregnant value, whereas

our values still fell at least one and one-half seconds below the average nonpregnant circulation time level.

In the toxemic group, the readings were in fair accord with the values obtained in the normal group. The series is too small to permit the drawing of any conclusions. In the rheumatic heart group, the five compensated patients showed circulation times well within normal limits.[38] The single patient who showed incipient failure clinically had moderately prolonged circulation times relative to the values we have established as "normal" for pregnancy. This prolongation was to be expected, as the slowing of blood velocity has been shown to be roughly proportional to the degrees of cardiac failure.[1]

Should the magnesium sulfate or ether circulation times be prolonged beyond the limits established herein for normal pregnancy, cardiac inadequacy should be suspected.

SUMMARY

1. Five hundred ninety-nine magnesium sulfate and 546 ether circulation times were studied in a group of 300 pregnant women, comprising 285 normal patients, 6 with rheumatic heart disease, and 9 with toxemias of pregnancy. One hundred twelve were primiparas and 188 multiparas, ranging in age from 17 to 40 years.

2. Five hundred forty-six magnesium sulfate circulation times were performed on 285 normal pregnant women. Three hundred twelve observations during the course of gestation averaged 9.9 seconds (5.5-15.2 seconds); 252 observations during the fourteen-day post-partum period averaged 10.4 seconds (6.8 to 15.2). A marked increase of blood velocity is observed throughout pregnancy and in the immediate post-partum period. During the first four months of gestation, a steady decrease in circulation time, relative to the nonpregnant level, is observed. Thereafter, until the thirty-fifth week, the circulation time remains practically constant. At this time, the circulation time increases moderately, maintaining its new level until the day of delivery and during the two weeks' post-partum period. At all times, the average magnesium sulfate circulation time remains far below the average nonpregnant level.

3. The magnesium sulfate circulation time is significantly shorter in primiparas than in multiparas, both ante partum and post partum.

4. Five hundred eleven ether circulation times were performed on 274 normal pregnant women. Two hundred ninety observations during the course of gestation averaged 5.4 seconds (3.0 to 9.2 seconds); 221 observations during the fourteen-day post-partum period averaged 5.5 seconds (3.2 to 8.4 seconds). The striking feature is that the ether circulation time is normal in value during the entire course of pregnancy and that the average circulation time is subject to practically no fluctuation.

5. The ether circulation time is slightly shorter in primiparas than in multiparas, both ante partum and post partum.

6. The magnesium sulfate and ether circulation times are normal during toxemias of pregnancy.

7. In compensated rheumatic heart disease, the magnesium sulfate and ether circulation times are within normal limits, and tend to increase with the onset of decompensation.

8. There is an incidence of 10.2 per cent of ether reactions of various types during and following ether circulation tests. The reactions include pain at the site of injection, pain along the course of the vein injected and into the shoulder, nausea and vomiting.

9. The right side of the heart is relatively unaffected during pregnancy; the left side carries the brunt of the "burden of pregnancy."

10. The changes in circulation time during pregnancy are correlated with the changes in cardiac output, oxygen utilization, blood viscosity, blood volume, and increased metabolic demands.

11. The use of ether as a circulation time agent during pregnancy apart from certain minor side reactions has no deleterious effects.

12. The use of magnesium sulfate as a circulation time agent in pregnancy is totally innocuous.

13. Any definite prolongation of either the magnesium sulfate or the ether circulation time beyond the limits established as normal for pregnancy in this work, should lead one to suspect the onset of cardiac decompensation.

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AN ATTEMPT AT ENDOCRINE CORRELATION AND THERAPY IN 125 CASES OF MENSTRUAL DISORDERS

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IN A series of 125 cases, an attempt was made to demonstrate whether there was any significant relationship between menstrual disorders and endocrinopathies. For the most part therapy was aimed at correcting an existing endocrinopathy with the hope of improving the menstrual irregularity. However, it was not assumed that the presence of a menstrual disturbance implied an associated endocrinopathy, nor that an endocrinopathy predicated a menstrual disorder. Moreover, the coexistence of an endocrinopathy and a menstrual irregularity was not considered as establishing a causal relationship between the two.

Voluminous data are available, revealing that menstruation is also influenced by many extrahormonal factors, as illustrated by the presence of amenorrhea in various anemias, aortic insufficiency, tuberculosis, nutritional deficiencies, and psychic disturbances.

Within recent years, numerous articles have appeared on the endocrine control of menstruation. Roentgen therapy has been utilized by many workers[1-5] in the form of low dosage irradiation to the pituitary and ovaries in the treatment of menstrual disorders, and profound alterations in the menstrual cycle were noted attending its use. Gonadotropic hormones were employed in the control of functional uterine bleeding.[6-8] Novak[9] and Israel[10] advocated the use of anterior pituitary-like hormones in dysmenorrhea, while others,[5b, 11, 12] have found these preparations variously effective in the treatment of secondary amenorrhea. With the advent and use of more potent gonadotropic extracts and sex sterols, results hitherto unobtainable have been observed. Davis and Koff[13] claim to have induced ovulation in the human being by utilizing the gonadotropic substance isolated from pregnant mare serum by Cole and Hart.[14] Kennedy and Shelton[15] obtained amelioration of menstrual dysfunction in a small series of cases treated with this substance. Siegler and Fein[16] were able to confirm the work of these authors. Kauffman[17] employed large dosages of estrogen followed by progestin to induce true menstruation, i.e. bleeding from a secretory endometrium, in castrates of even long standing. The same author[18] also induced uterine bleeding in cases of secondary amenorrhea with large dosages of estrogen. Dunn[19] reported on the induction of menstruation in amenorrheas of various duration by the use of anterior pituitary extracts and estrogens. It was probable that in these cases the bleeding was from a proliferative endometrium and that the estrogen was essentially responsible for the results obtained. Frank and others,[20] however, were unable to obtain any significant effects with even high dosages of estrogen in secondary amenorrheas. Diethylstilbestrol, an estrogenic substance synthesized by Dodds, Goldberg, Lawson and Robinson,[21] was found to be almost as potent orally as parenterally. Many authors,[22-24] however, have noted a rather high percentage of untoward side reactions, principally manifested by gastrointestinal disturbances, attending its use. Uterine bleeding following the withdrawal of this drug was frequently observed. Karnaky[25] recommended its use in high dosages in the control of functional uterine bleeding. Mocquot and Moricard[26] were among the first to use androgens in the treatment of gynecic disturbances. These authors, Salmon,[27] Shorr, Papanicolaou and Stimmel,[28] and others have utilized testosterone propionate beneficially in the

treatment of the menopause. Greenblatt and Torpin[29] have recently published a confirmation of the findings of these authors and other investigators on the amelioration of the symptoms in menopause, premenstrual tension, menometrorrhagia and hypermenorrhea with the use of androgens. However, they advised employing small doses, as many undesirable effects, such as hirsutism, enlargement of the clitoris, facial acne, and a deepening of the voice, had been reported following the use of large doses of testosterone propionate, by Loeser,[30] Foss,[31] Geist, Salmon and Gaines,[32] and Greenhill and Freed.[33] Israel[34] advocated the use of progesterone in premenstrual tension because he believed there was a corpus luteal deficiency in this syndrome.

Much of the treatment carried out by these investigators was highly empirical and the desired results were often not obtained. It was for this reason, in part, that an attempt was made to obtain some standard which would tend to suggest a more accurate therapeutic approach.

METHODS

A careful clinical evaluation of the patient, based on a thorough history, physical examination, and appropriate laboratory studies, was carried out in arriving at a differential endocrine diagnosis. A quantitative estimation of urinary prolans and estrogens was made in most cases. The prolans were assayed in a twenty-four-hour postmenstrual specimen, and the estrogens in a twenty-four-hour premenstrual specimen, in women with cyclic bleeding. In amenorrhea, a forty-eight-hour specimen of urine was used for both determinations. In the intervals in the cycle designated for collection, it was found that the respective hormones were excreted at a more constant level and in sufficient amounts to serve as some standard for evaluation of the results.

The urinary prolans were extracted by utilizing essentially the method of Katzman and Doisy.[35, 36] A fresh refrigerated specimen of urine was precipitated with benzoic acid, and after the precipitate was removed, was again precipitated by tannic acid. The precipitates were combined and the precipitants were removed by successive washings with acetone. An aqueous solution of the precipitate was then biologically assayed in twenty-one-day-old immature female rats, according to the method of Collip, in which a unit is the minimum amount of substance which when administered subcutaneously daily for three days will produce vaginal estrus within one hundred and twenty hours. By this method, normal values for urinary prolan were found to range between 40 and 60 rat units in twenty-four hours in women between the ages of 18 and 38 years. The estrogens were removed after a two-hour acid hydrolysis of the urine, according to the method of Gallagher, Koch and Dorfman,[37] by continuous extraction with benzene. The solvent was subsequently removed by distillation under reduced pressure. The residue was dissolved in about 100 c.c. of ethyl ether and extracted ten times by shaking with 50 c.c. quantities of 10 per cent sodium hydroxide. About 95 per cent of the estrogenic substances were contained in the alkali. This fraction was then acidified and re-extracted with ether; the latter was removed and the residue dissolved in sesame oil, with the removal of the last traces of solvent by heat. The oil solution with the resultant estrogenic material was then biologically assayed in spayed adult female rats. A positive test was considered as reestablishment of estrus, as evidenced by the characteristic cellular changes in the vaginal smear. By this procedure normal values of 60 to 90 rat units were found to be excreted per diem in women from the ages of 18 to 38 years. Blood values for these hormones were not determined routinely because the results were not reproducible. The other laboratory examinations included a five-hour glucose tolerance test, blood calcium and phosphorus, basal metabolic rate, cholesterol, and Volhard fluid-retention test where indicated.

The menstrual disorders encountered were divided into the following groups: hyper- and hypomenorrhea, amenorrhea (primary and secondary), dysmenorrhea, polymenorrhea, menorrhagia, metrorrhagia, and premenstrual tension. The terms as used here were essentially as defined by Fluhmann.[38] The endocrinopathies encoun-

tered were classified as follows: hypopituitarism, hypogonadism, hypothyroidism, hyperpituitarism, hyperthyroidism, hypoadrenia, and virilism. The diagnosis was based on the characteristic findings in the history, symptomatology, and laboratory examinations.

RESULTS

In this series of 125 cases, 120, or 96 per cent, exhibited endocrinopathies, and there was an incidence of 1.7 menstrual disorders per patient, or 215 menstrual irregularities. This high percentage was encountered, first, because the patients were referred primarily as endocrine cases, and second, because borderline cases of menstrual and endocrine disturbances were included. However, the high incidence of menstrual disorders in this series indicated that the hormonal control of menstruation was etiologically important.

TABLE I. INCIDENCE OF MENSTRUAL DISORDERS

DISORDER	NO. CASES	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Dysmenorrhea	65	30.0%	52.0%
Oligomenorrhea	44	20.0%	35.0%
Hypomenorrhea	32	15.0%	25.0%
Premenstrual tension	24	11.2%	19.2%
Amenorrhea	19	8.9%	15.2%
Menorrhagia	11	5.3%	8.8%
Hypermenorrhea	10	4.7%	8.0%
Polymenorrhea	6	2.9%	4.8%
Metrorrhagia	4	2.0%	1.6%
Totals	215	100.0%	169.6%

The most common menstrual disorder encountered was dysmenorrhea, with an incidence of 52 per cent (Table I). In these 65 cases of dysmenorrhea, about one-third were associated with a pelvic abnormality; O'Donel Browne[39] reported about 75 per cent of the cases of dysmenorrhea he observed which were explainable on a basis of a pelvic abnormality. Brown[40] in 31,309 cases found an incidence of 45 per cent of dysmenorrhea. Oligomenorrhea, with an incidence of 35 per cent, was the second most frequent menstrual disturbance found (Table I). Infantile uteri were noted in over half of these patients. The incidence of hypomenorrhea was 25 per cent (Table I). Infantile uteri also were frequently found in this group. Of less frequency was the occurrence of premenstrual tension, amenorrhea, menorrhagia, and metrorrhagia, all of which represented only about 38 per cent of the total menstrual irregularities observed, or about one-fourth. The occurrence of 169.6 per cent instances of menstrual disorders in this group was due to the existence of more than one menstrual disorder in the majority of the cases.

Of the 120 patients presenting endocrine stigmas, 160 endocrinopathies were exhibited (Table II). Hypopituitarism, which was by far the most frequently encountered condition, showed the same relative incidence of menstrual disturbances as observed in the group as a whole (Table III). In hypogonadism, amenorrhea

TABLE II. INCIDENCE OF ENDOCRINOPATHIES

DIAGNOSIS	NO. CASES	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypopituitary	70	43.8%	58.3%
Hypogonad	37	23.1%	30.8%
Hypothyroid	36	22.5%	30.0%
Hyperpituitary	7	4.4%	5.8%
Hyperthyroid	4	2.5%	3.3%
Hypoadrenia	3	1.85	2.3%
Virilism	3	1.85	2.3%
Totals	160	100.00	132.8

TABLE III. THE INCIDENCE AND RELATION OF MENSTRUAL DISORDERS TO ENDOCRINOPATHIES

DISORDER	HYPO-PITUITARY		HYPOGONAD		HYPO-THYROID		HYPER-PITUITARY		HYPER-THYROID		HYPO-ADRENIA		VIRILISM		NORMAL		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Dysmenorrhea	41	33.1* 44.5†	21	30.0 22.8	18	28.0 19.9	3	23.1 3.2	3	42.8 3.2	2	40.0 2.1	0	– –	4	36.3 4.3	92	31.1* 100.0†
Oligomenorrhea	24	19.4 37.5	17	24.3 26.6	16	25.0 25.0	2	15.4 3.1	1	14.3 1.55	1	20.0 1.55	2	100.0 3.1	1	9.0 1.6	64	21.7 100.0
Hypomenorrhea	19	15.3 46.3	5	7.0 12.2	10	16.0 24.4	3	23.0 7.3	0	– –	2	40.0 4.9	0	– –	2	18.6 4.9	41	13.9 100.0
Premenstrual tension	12	9.6 36.4	10	14.3 30.3	6	9.1 18.2	1	7.7 3.0	1	14.3 3.0	0	– –	0	– –	3	27.1 9.1	33	11.1 100.0
Amenorrhea	9	7.3 37.5	11	15.7 45.8	2	3.0 8.3	1	7.7 4.2	0	– –	0	– –	0	– –	1	9.0 4.2	24	8.1 100.0
Menorrhagia	4	3.2 23.5	3	4.3 17.8	7	10.9 41.1	2	15.4 11.8	1	14.3 5.8	0	– –	0	– –	0	– –	17	5.7 100.0
Hypermenorrhea	5	4.0 41.7	2	2.8 16.7	4	6.4 33.3	1	7.7 8.3	0	– –	0	– –	0	– –	0	– –	12	4.1 100.0
Polymenorrhea	4	3.2 66.6	1	1.6 16.7	1	1.6 16.7	0	– –	0	– –	0	– –	0	– –	0	– –	6	2.0 100.0
Metrorrhagia	2	1.7 66.7	0	– –	0	– –	0	– –	1	14.3 33.3	0	– –	0	– –	0	– –	3	1.0 100.0
Normal	4	3.2 100.0	0	– –	0	– –	0	– –	0	– –	0	– –	0	– –	0	– –	4	1.3 100.0
Total	124	100.0 41.8	70	100.0 23.6	64	100.0 21.6	13	100.0 4.4	7	100.0 2.4	5	100.0 1.8	2	100.0 0.7	11	100.0 3.7	296	100.0 100.0

*Upper figures represent incidence of endocrinopathies in menstrual disorders.
†Lower figures represent incidence of menstrual disorders in endocrinopathies.

and premenstrual tension were more frequently found. In the cases of hypothyroidism there was an increased incidence of menorrhagia. Of the remaining endocrinopathies and nonendocrine cases, there were too few patients to justify any conclusion.

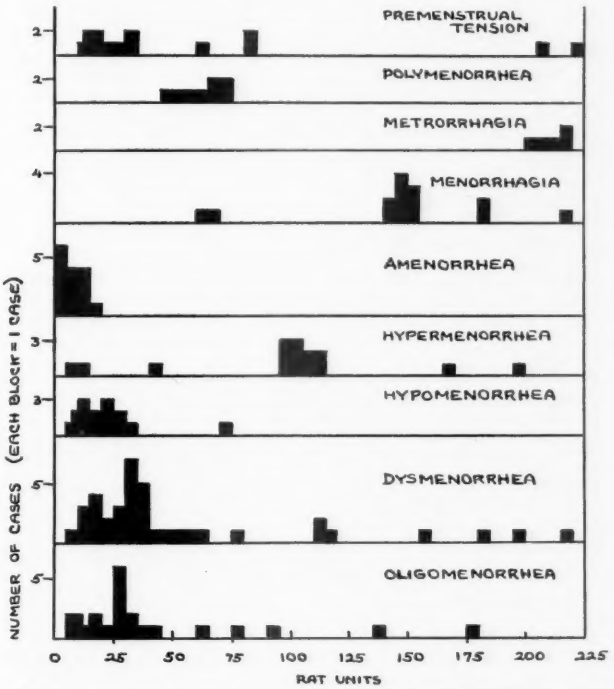

Fig. 1.—Urinary excretion of estrogens in menstrual disorders.

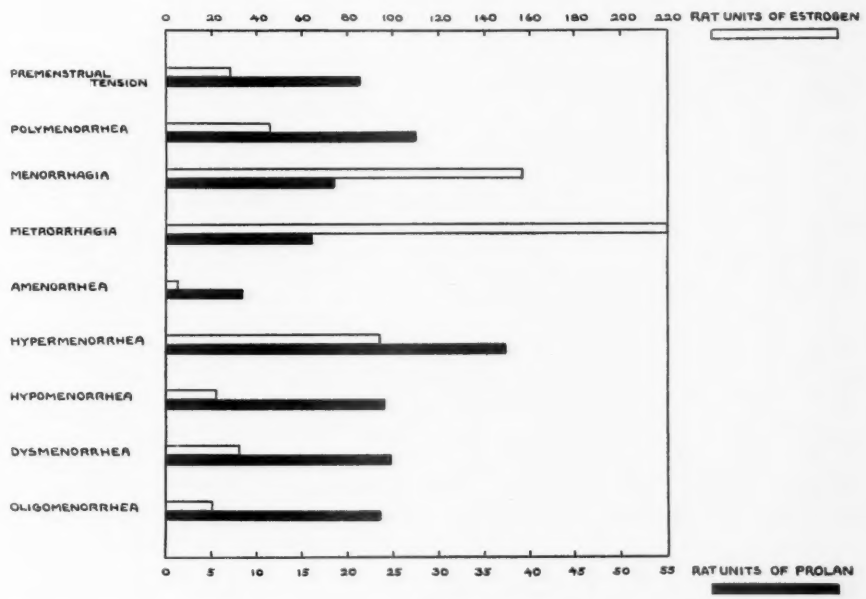

Fig. 2.—Mean rates of urinary prolan and estrogen excretion in menstrual disorders.

Of this entire series of 125 patients, 63, or 50 per cent, were obese (Table IV). The obesity was most prevalent in those patients with dysmenorrhea, oligomenorrhea, and hypomenorrhea (almost 75 per cent). Sixty-two of these 63 cases of obesity, or 98 per cent, were associated with endocrinopathies (Table V), of which 50 per cent were hypopituitary, 30 per cent hypothyroid, and 13 per cent hypogonad. Fluid retention was considered significant if there was more than 25 per cent retained in the four-hour test. Forty per cent of the hypopituitary cases, 50 per cent of the hypothyroid cases, and 33 per cent of the hypogonad cases had water retention. Forty-three per cent of the cases of dysmenorrhea, 53 per cent of the cases of oligomenorrhea, 31 per cent of the cases of hypomenorrhea, 55 per cent of the cases of premenstrual tension, and 100 per cent of the cases of hypermenorrhea had fluid retention.

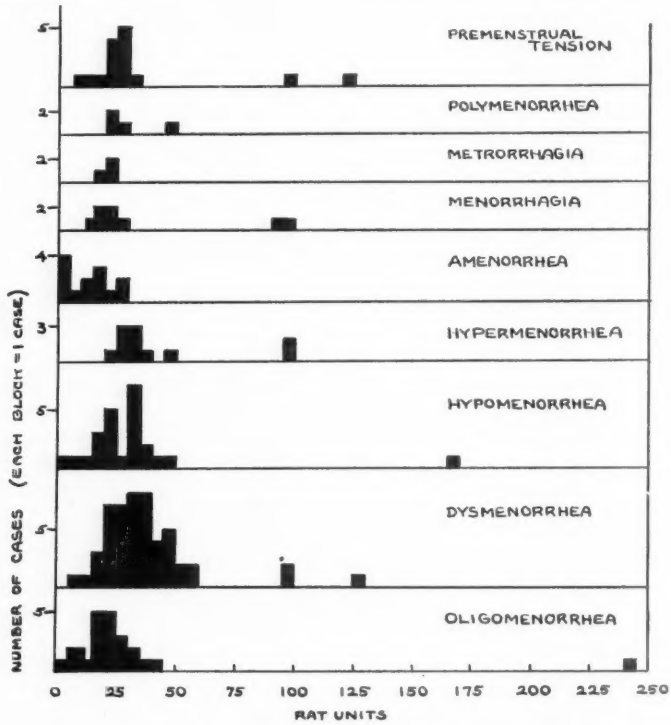

Fig. 3.—Urinary excretion of prolan in menstrual disorders.

There was a correlative trend between increased estrogen excretion and excessive bleeding. Mean values of estrogen excretion varied from 160 rat units in menorrhagia to over 200 rat units in metrorrhagia (Fig. 2); whereas in amenorrhea, oligomenorrhea, and hypomenorrhea, there was a marked diminution in the estrogen output, with values of 20 rat units or less (Fig. 1). In amenorrhea there was a marked reduction in the excretion of urinary prolans. A diminution in urinary prolan was also observed in dysmenorrhea, oligomenorrhea, hypomenorrhea, and less significantly in menorrhagia and metrorrhagia (Fig. 3). Similarly, a reduction of urinary prolans was observed in the cases of hypopituitarism, hypogonadism, and hypothyroidism, which corresponded with the assays encountered in the menstrual disorders most common to these groups. There was a diminution in urinary estrogens in the cases of hypopituitarism and hypogonadism.

TREATMENT

Where possible, treatment was aimed at re-establishing a normal level of endocrine function by attempting to stimulate the deficient gland.

TABLE IV. OBESITY IN MENSTRUAL DISORDERS

DIAGNOSIS	NO. OF CASES	INCIDENCE	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypomenorrhea	There was more than one menstrual disorder in some of the patients	16	18.2%	12.8%
Hypermenorrhea		4	4.6%	3.2%
Oligomenorrhea		20	22.7%	16.0%
Amenorrhea		6	6.8%	4.8%
Polymenorrhea		1	1.1%	0.8%
Menorrhagia		4	4.6%	3.2%
Metrorrhagia		1	1.1%	0.8%
Dysmenorrhea		29	32.9%	23.2%
Premenstrual tension		7	8.0%	5.6%
Totals	63	88	100.0%	70.4%

TABLE V. OBESITY IN ENDOCRINOPATHIES

DIAGNOSIS	NO. CASES	INCIDENCE	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypopituitary	There was more than one endocrinopathy in some of the patients	39	50.7%	32.3%
Hyperpituitary		4	5.2%	3.3%
Hypothyroid		23	30.0%	19.3%
Hyperthyroid		–	–	–
Hypogonad		10	13.0%	8.3%
Hypoadrenia		–	–	–
Virilism		1	1.1%	0.8%
Totals	62	77	100.0%	64.0%

In most cases where a pelvic abnormality existed, surgical or mechanical correction was initially attempted. The success of this corrective procedure was noted so that the improvement would not be attributed to other forms of therapy. In patients with cyclic bleeding where there was a diminution in estrin and prolan, as encountered in dysmenorrhea, oligomenorrhea, hypomenorrhea, and premenstrual tension, therapy consisted of, first, a preliminary course of estrogen if the uterus was infantile, in an attempt to promote uterine growth. In most instances this could be accomplished by the administration of 10,000 rat units of a-estradiol benzoate or 1 mg. diproprionate intramuscularly twice a week for two to four weeks, as guided by pelvic examination. Second, when the uterus had attained approximately normal size, the estrogen treatment was interrupted and was usually followed in a few days by withdrawal-uterine bleeding. Five days after the last injection, if there was no bleeding, and immediately after the cessation of flow if there was bleeding, or in patients with normal uteri, therapy consisting of 300 rat units (Collip) of anterior pituitary gonadotropic hormone (A.P.) and 500 rat units (Collip) of chorionic gonadotropic hormone (A.P.L.) mixed in the same syringe was administered every other day until the fourteenth day of the cycle. Half of this dose was administered daily in a group of patients during the same period of time, with the hope of producing a more physiologic rate of absorption, but no added benefit was observed. This treatment was repeated for two subsequent cycles postmenstrually. As soon as improvement was noted, treatment was withdrawn and the patient was observed to determine how long she remained free of symptoms. This type of treatment was not carried out

for more than three cycles without interruption, because not infrequently, even though no amelioration of symptoms was observed during the course of therapy, on its withdrawal, an improvement would be noted.

In secondary amenorrhea (nonclimacteric) if the uterus was small, a preliminary course of estrogen therapy as suggested above was carried out, followed after five days by 5 mg. of progesterone every other day for four to six injections. This often resulted in bleeding from a secretory endometrium or a true menstruation. If the amenorrhea was of long standing, it was usually necessary to give more intensive estrogen therapy to stimulate uterine growth. Following bleeding, postmenstrual anterior pituitary gonadotropic hormone and chorionic gonadotropic hormones were administered as outlined above. Often, after several months of postmenstrual therapy, the uterus might again become small, necessitating further priming with estrogenic substances. In those cases where the uterus was of normal size, treatment consisted of administering 600 rat units of anterior pituitary gonadotropic hormone every other day for one to two weeks, followed by 500 rat units chorionic gonadotropic hormone every other day for one to two weeks. This was followed by one week without therapy. At the end of this week, if menses had not ensued, the same therapy was repeated. Subsequently it was found that it was more advantageous to administer the anterior pituitary gonadotropic hormone and chorionic gonadotropic hormones in combination instead of successive intervals. After menses was established, the usual regimen of postmenstrual combination anterior pituitary gonadotropic hormone and chorionic gonadotropic hormone up to the fourteenth day was carried out.

In menorrhagia where an excess of estrogen was usually excreted, treatment was designed to inhibit the excess of this hormone. This was accomplished by either administering progesterone premenstrually, starting about five to seven days before the expected period and giving 5 to 10 mg. a day, or utilizing the same principle by administering progressively increasing doses of chorionic gonadotropic hormone five to seven days before the expected period; e.g., 100 rat units (Collip) the first day, 200 R.U. the second day, 300 R.U. the third day, 400 R.U. the fourth day, 500 R.U. the fifth day, etc., giving the last injection on the first day of the period. Attempts to accomplish this same result with androgens were equally effective, but resulted in undesirable side actions. The value of utilizing large dosages of estrogen in cases of excessive bleeding as advocated by some authors[25] is probably based on its inhibitory effect on the pituitary and ovary. In those cases where the menorrhagia was associated with hypothyroidism, the use of thyroid in increasing doses as tolerated was employed daily intermenstrually.

In hypermenorrhea, the treatment is similar to that employed in menorrhagia. However, in addition, therapy consisting of 500 R.U. of chorionic gonadotropic hormone was administered every other day until the fourteenth day of the cycle, starting with the third or fourth day, while menstruation was still taking place.

In polymenorrhea, 500 R.U. of chorionic gonadotropic hormone was administered every other day until the fourteenth day of the cycle, starting at the third or fourth day. In those patients in whom bleeding took place between the fourteenth and the twenty-fourth day, the chorionic gonadotropic hormone was administered throughout the entire cycle. When the cycle had been prolonged in this manner, the drug was again administered in the same dose postmenstrually during the fourth to the fourteenth day, to prolong the life of the corpus luteum.

In metrorrhagia, most of the patients manifested uterine and ovarian pathology and responded to surgical intervention. In the remaining patients, chorionic gonadotropic hormone therapy was administered throughout the cycle.

CASE REPORTS

CASE 1.—Miss S. B. (dysmenorrhea), aged 16 years, menarche at 13 years, cycle three to four months, interrupted flow for four days. Two years ago dysmenorrhea became more severe with lancinating pain in lumbosacral region for one week premenstrually.

Pelvic examination was normal, basal metabolic rate, plus 2; water retention, 42 per cent.

Assay: 12 R.U. of estrogen.

Therapy: 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day from the fifth to the fourteenth day of the cycle. She menstruated on the thirtieth day, good flow, less pain. The same treatment was repeated following the period. She menstruated twenty-eight days later with no pain, four-day flow. She was treated similarly for third cycle, followed by a period twenty-one days later with no pain. She has had no therapy for 6 months, has a twenty-eight-day cycle, four-day flow, and no pain.

CASE 2.—Mrs. B. O. (oligomenorrhea), aged 23 years, menarche at 14 years, forty- to ninety-day cycle, two-day scant flow (hypomenorrhea), was hypogonad with infantile uterus.

Assays: 20 R.U. of prolan, 12 R.U. of estrogen per diem.

Therapy: She was given 10,000 R.U. of estradiol diproprionate twice a week for two weeks. Two days after cessation of treatment, she had a four-day good flow. Postmenstrually she received 300 R.U. of anterior pituitary every other day until fourteenth day of cycle. At thirty-five days there was still no flow; uterus had regressed. She was given 20,000 R.U. of estrogen in two injections. Menses followed. Then she received 300 R.U. of anterior pituitary and 200 R.U. of chorionic gonadotropic hormone until fourteenth day. Bleeding occurred on thirtieth day. The latter treatment was repeated after cessation of flow, and next period occurred on thirty-second day. After no treatment for two months, period again became delayed. Postmenstrual anterior pituitary and chorionic gonadotropic hormones in the same dosage as previously, resulted in a period thirty-one days later. The treatment was repeated the following month and menses started on twenty-ninth day. She has had no therapy for five months during which time menses occurred twenty-eight to thirty-one days with good flow.

CASE 3.—Mrs. H. S. (hypomenorrhea), aged 30 years, menarche at 13 years, twenty-eight- to twenty-nine-day cycle, twenty-four-hour scant flow with premenstrual breast engorgement, a hypopituitary-hypogonad with an infantile uterus.

Assays: 20 R.U. of prolan, 15 R.U. of estrogen.

Therapy: She was given 10,000 R.U. of estradiol benzoate twice a week for two weeks premenstrually. Postmenstrually she received 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone until the fourteenth day of the cycle for 6 cycles. Her cycle is the same and she has a three- to five-day good flow. Her uterus has remained normal in size and the flow is normal after seven months without therapy.

CASE 4.—Mrs. E. B. (amenorrhea), aged 17 years, menarche at 16 years, had 3 normal periods at thirty-day intervals with four-day flow. After appendectomy she became amenorrheic for nine months. She was a hypopituitary-hypogonad with an infantile uterus.

Assays: (48-hour specimen) 5 R.U. of prolan, 10 R.U. of estrogen.

Therapy: Consisted of 10,000 R.U. of estradiol benzoate three times a week for two weeks. Nineteen days after onset of treatment uterus was normal size. She then received 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day for three weeks. Ten days after the last injection bleeding began; the flow lasted four days. She was then given 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day until the fourteenth day. She had another normal period forty days after the last. Therapy was repeated and the period was delayed; patient was found to be pregnant. She went to term and pursued an uneventful course.

CASE 5.—Miss I. B. (menorrhagia), aged 25 years, menarche at 12 years, twenty-eight-day cycle, seven- to eight-day profuse flow preceded by severe migraine, hypothyroid. Basal metabolic rate was minus 19; water retention, 32 per cent.

Assays: 90 R.U. of prolan, 160 R.U. of estrogen.

Therapy: She was given 1 gr. of thyroid t.i.d. with some reduction in flow but had persistent headaches. She was then given 100 R.U. of pregnancy urine extract (P-D) on the twenty-fourth day, 200 R.U. on the twenty-fifth day, 300 R.U. on the twenty-sixth day, 400 R.U. on the twenty-seventh day, and 500 R.U. on the first day of menses. There was a marked reduction in flow and no headaches. She was given 1 gr. of thyroid t.i.d. postmenstrually until the fourteenth day and pregnancy urine extract as previously from the twenty-fourth day of the cycle, for three cycles. After ten months without therapy, the flow is normal and there have been no headaches.

CASE 6.—Miss M. S. (polymenorrhea), aged 16 years, menarche at 13 years, twenty-one-day cycle, seven-day good flow with severe dysmenorrhea which was improving spontaneously. Hypopituitary infantilism. Pelvic examination was unsatisfactory. Basal metabolic rate was minus 2; glucose tolerance test, C.B.C.; and urine normal. Cholesterol 182 mg.

Assays: 20 R.U. of prolan, 35 R.U. of estrogen.

Therapy: 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone until fourteenth day of cycle. This was followed by three periods at thirty-two- to thirty-five-day intervals with a five-day good flow and one to two days of staining with no dysmenorrhea. For six months without therapy the cycle has been thirty to thirty-two days with a five-day flow.

DISCUSSION

In a large series of cases referred to this clinic for endocrine study, 125 patients complaining of various menstrual irregularities were analyzed for the purpose of demonstrating a possible relationship between the endocrinopathy, if present, and the menstrual disturbance. The incidence of endocrine stigmas was, therefore, exceedingly high, occurring in 96 per cent of the cases. Attempts to correlate the association of a specific menstrual disorder with a specific endocrinopathy, and vice versa, revealed a significant relationship (Table III). In the majority of instances, dysmenorrhea, oligomenorrhea, hypomenorrhea, and premenstrual tension were most prevalent in hypopituitary cases. Amenorrhea was encountered most frequently in hypogonadal cases. Menorrhagia predominated in hypothyroidism, while hypermenorrhea, polymenorrhea, and metrorrhagia occurred most often in hypopituitarism, but the relationship was less significant because of the small number of patients. The chief menstrual complaints in most of the endo-

crinopathies were dysmenorrhea, oligomenorrhea, hypomenorrhea, premenstrual tension, and amenorrhea in the order named; this group constituting about 85 per cent of the menstrual disturbances. It was not the intention of this paper to attribute an underlying endocrinopathy as a cause for all menstrual irregularities, for the data were collected on the basis of the endocrinopathy and not the menstrual disorder. However, the exceedingly high incidence of menstrual disorders in patients with endocrine stigmas was considered more than a coincidence. It may well be that the presence of an endocrinopathy predisposes a menstrual disturbance. Additional data which are being accumulated may lend strength to this supposition. Data tabulated on patients worked up in a gynecology clinic from an endocrine viewpoint would do much to bring the loose ends of this problem together.

The hormone assay was found to be of considerable value in the diagnosis and treatment of these menstrual irregularities, particularly when correlated with the other laboratory procedures.

In the majority of cases, the patients were treated on the basis of the endocrine findings. Only five types of drugs were necessary to carry out optimal treatment in most cases. These were as follows: (1) Prolan A, in which the source was either anterior pituitary gonadotropic hormone or pregnant mare's serum; (2) prolan B, in which chorionic gonadotropic hormone was employed; (3) estrogenic hormone, which was utilized chiefly as estradiol benzoate or estradiol diproprionate, (4) corpus luteum extract in the form of progesterone; and (5) thyroid hormone prescribed in the form of desiccated thyroid gland substance.

TABLE VI. RESULTS OF TREATED CASES

DIAGNOSIS	NO. OF CASES	DURATION OF TREATMENT		TIME OF RESPONSE		EXTENT OF IMPROVEMENT				FAILURE		STILL IMPROVED WITHOUT THERAPY	
		MO.	AVER.	MO.	AVER.	MARKED		SLIGHT		NO.	%	NO.	%
						NO.	%	NO.	%				
Dysmenorrhea	33	1-12	3.7	1-3	2.9	27	66.6	5	15.2	6	18.2	18	54.5
Oligomenorrhea	19	1-12	4.4	1-4	3.1	13	68.4	1	5.3	5	26.3	10	53.0
Hypomenorrhea	17	1-7	3.7	1-4	2.2	12	71.0	2	12.0	3	17.0	9	53.0
Premenstrual tension	22	3-9	3.5	1-4	2.0	14	63.6	3	13.6	5	22.8	5	23.0
Amenorrhea	9	2-12	4.5	1-6	3.8	7	77.7	2	22.3	0	0	8	89.0
Menorrhagia	2	1-3	2.0	1-2	1.6	2	100	0	0	0	0	2	100
Hypermenorrhea	5	1-4	3.2	1-3	2.8	4	80.0	0	0	1	20.0	4	80.0
Polymenorrhea	3	1-5	3.0	1-3	2.5	3	100	0	0	0	0	3	100
Metrorrhagia	2	1-4	2.5	1-3	2.0	2	100	0	0	0	0	2	100
Totals	112					79	70.5	13	11.6	20	18.1	61	54.4

Utilizing treatment based on correcting the existing endocrinopathy, it was found that over 50 per cent of the patients with menstrual disturbances (Table VI) were free of symptoms even after treatment was withdrawn, although it is possible that some of these patients may yet have a recurrence. Only 18.1 per cent of the patients treated in this manner failed to respond at all, and 70 per cent of the patients improved markedly with the elimination of the menstrual irregularity, although about 16 per cent of these subsequently relapsed. In dysmenorrhea,

oligomenorrhea, and hypomenorrhea, which constituted the major types encountered, over 50 per cent are still free of symptoms, even after cessation of treatment (Table VI).

SUMMARY

1. One hundred and twenty-five cases of menstrual disorders were presented.

2. These were referred primarily as endocrine cases and were studied and treated on this basis.

3. In this group a significant correlation was found to exist between menstrual irregularities and endocrinopathies.

4. Endocrine therapy resulted in marked improvement in over 50 per cent of the patients treated.

Our appreciation is extended to Dr. W. H. Stoner of Schering Corporation, Bloomfield, N. J., for his generous supply of estradiolbenzoate (progynon-B) and progesterone (proluton), estradiol dipropionate (progynon, D. P.), pregnant mare's serum (anteron).

The chorionic gonadotropic hormone (A. P. L.) and the anterior pituitary gonadotropic hormone (Gonadotropic Factor) used in these experiments were manufactured by Ayerst, McKenna & Harrison (United States), Ltd.

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THE TREATMENT OF ABNORMAL UTERINE BLEEDING WITH ANDROGENS

Therapeutic Evaluation of Testosterone Propionate, Methyl Testosterone, Ethinyl Testosterone and Androgen Implantation

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DURING the past three years, several enthusiastic reports have appeared on the use of synthetic male hormone (testosterone propionate) in the treatment of functional bleeding. To those who are interested in the problem of abnormal uterine bleeding and have been following the literature dealing with this subject, these reports sound an encouraging and welcome note. For, in spite of numerous clinical, morphologic, and hormonal studies performed in the past ten years, both the etiology and therapy of functional uterine bleeding still remain unsolved problems. A variety of theories and therapeutic agents have been in vogue at various times, but none has withstood critical analysis. It is, therefore, of considerable practical, as well as theoretical, importance to examine, critically, the results obtained with testosterone propionate.

It does not fall within the province of this paper to review and attempt to correlate the vast literature dealing with the biologic effects of androgens in laboratory animals. It is worthy of note, however, that the use of testosterone propionate as a therapeutic agent in gynecology is generally based on the observation that testosterone suppresses the vaginal (estrus) smear reaction in rats and mice.[7, 31, 57, 72] Several authors have concluded therefrom that androgens are antagonists of the estrogens. What apparently has been overlooked is that, during the period of (testosterone induced) estrus suppression, the vaginal mucosa is markedly mucinified; that the endometrium at the same time reveals proliferative and, in some cases, progestational changes; and that the muscular coats of the uterus and vagina are hypertrophied.[15, 38, 39, 50, 51] So that the "antagonism" between estrogens and androgens, upon which the therapeutic use of testosterone in women is based, is actually confined to one phase of the estrogen action in rodents viz., the cornification of the vaginal mucosa. In other respects, however, testosterone either simulates, complements, or augments the action of the estrogens. It is interesting to note that, in immature female rats and mice, testosterone exhibits both gynecogenic* and androgenic properties. Thus it causes premature opening and cornification of the vagina[61] and hypertrophy of the uterus, in addition to follicle growth and corpora lutea formation in

*The term "gynecogen" refers to the female sex hormones, i.e., both the estrogens and progesterone.

the ovaries,[49, 53, 60, 61, 70] as well as growth of the clitoris and preputial glands.[61] Continued administration of testosterone, however, results in eventual atrophy of the ovaries.[45, 47] As regards the action of testosterone on the pituitary, there is evidence to suggest that, in adult female rats, testosterone inhibits,[2, 52, 73] whereas, in immature rats, it stimulates[49, 60, 61] the gonadotropic activity of the hypophysis. Furthermore, menstruation has been delayed and ovulation inhibited in monkeys[30, 76] and rabbits[12] with testosterone. It appears, therefore, that when administered to female animals, testosterone exhibits a variety of properties, evoking gynecogenic and androgenic responses, the relative intensity of the component effects varying with the species and the age of the animal and the dosage and duration of the hormone administration. It would, therefore, hardly seem justifiable to base the rationale for the use of testosterone, as a therapeutic agent in women, upon a single one of its biologic properties (viz., the ability to suppress the vaginal cornification reaction in rats and mice) and ignore the other properties which biologically can be considered as antithetical and could, therefore, quite logically permit of diametrically opposite conclusions. It seems to us to be both illogical and unnecessary to seek, in animal experiments, a rationale for the use of androgens in the treatment of abnormal uterine bleeding, when a physiologic basis for their use can be found in the biologic effect which testosterone evokes in human females. Thus it has been shown that testosterone propionate, if given in sufficient amounts to woman, inhibits the secretion of gonadotropic hormone by the hypophysis,[62] suppresses ovulation[24] and menstruation[21, 25, 40, 55, 56] and abolishes temporarily the normal proliferative and secretory phenomena of the endometrium, reducing the latter to a state of involution.[21, 25, 63] In cyclical women, in contrast to rodents, the action of testosterone propionate appears to be monophasic, viz., antigynecogenic. It was felt, therefore, since testosterone inhibits both the gonadotropic activity of the pituitary (which appears to be the primary factor in the cycle of events which culminates in uterine bleeding) and the endometrium (which is the end organ involved in the bleeding process) that possibly abnormal uterine bleeding could be controlled by utilizing this antigynecogenic property of testosterone.

Here we wish to present: (a) our experience (extending over a period of over three years) with 61 cases of abnormal uterine bleeding treated with testosterone propionate; (b) recommendations as to the optimal dosage; (c) safeguards to be employed in order to avoid the masculinization phenomena; (d) some theoretical concepts in regard to the etiology of functional bleeding and the physiologic role of androgens in the sex hormone organization of the human female; and (e) a preliminary report on the value of methyl testosterone, ethinyl testosterone and androgen implantation.

LITERATURE

In 1938, Loeser[40] reported good results in a series of 10 cases of menorrhagia treated with testosterone propionate. Five of these were apparently functional and 5 had small fibroids. The dose used varied from 500 to 1,500 mg., given during three to four weeks. Unfortunately, the author did not state what the results were

after discontinuation of the treatment. At about the same time, Foss[19] reported a series of 6 cases of meno- and metrometrorrhagia treated with testosterone propionate. The doses used varied from 200 to 2,200 mg. Analysis of the 6 case histories which are presented reveals that only 2 could be considered as representing satisfactory results. One patient was 45 years of age, and, after 200 mg. of testosterone, developed amenorrhea and menopausal symptoms. The other was 18 years of age and had a history of menometrorrhagia alternating with amenorrhea. On the basis of the results obtained in an additional 10 cases, the author concluded, however, that testosterone is an effective therapeutic agent in the treatment of meno- and metrorrhagia.

In the same year, Geist, Salmon and Gaines[25] published a series of 25 cases of menometrorrhagia (21 functional and 4 associated with small uterine myomas). The investigation included a study of the effect of testosterone propionate upon the endometrium in correlation with its clinical effects. The significance of this report is three-fold: first, the postherapy period of observation which revealed the persistence of the therapeutic effect, in some cases for as long as five months after cessation of the treatment; second, the striking regressive changes induced in the endometrium followed by restoration to the normal pattern; and, third, the warning in regard to the induction of masculinization phenomena when large doses of testosterone are used. The dosage ranged from 300 to 1,000 mg. per month. The abnormal bleeding was controlled in all but 2 cases, during a period of observation extending up to five months. Four of the patients developed mild facial hirsuties, 3 hoarseness and one acne.

In 1938, Beclere[6] treated 14 patients with menorrhagia (6 premenopausal, 7 associated with chronic adnexal disease, and 1 with a submucous fibroid). He was able to control the excessive bleeding in all but 2 cases (chronic adnexitis), using small doses (1 to 2 injections of 25 mg. each, per month). In 1939, the Mazers[46] obtained good results in 68 per cent of a series of 38 cases (29 metrorrhagia and 9 menorrhagia), using comparatively small doses (30 to 300 mg. per month). With this dosage no masculinization phenomena were produced.

MATERIAL

The present study was conducted on a series of 61 cases of abnormal uterine bleeding. In this series are included 25 cases which had been previously reported in 1938.

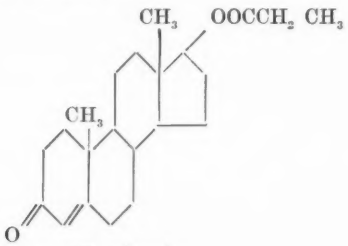
In 45 cases examination failed to reveal palpable organic disease, and the cases were accordingly classified as "functional." In 15 cases, small uterine myomas were present. These varied in size, the largest uterus approximating the size of a four months' gravid uterus. There was one case of adenomyosis of the uterus with menorrhagia. Of the 45 patients with functional bleeding, 33 were between the ages of 40 and 53 years; 11 were from 21 to 39 years of age. One patient was aged 14 years. The patient with adenomyosis was 36 years of age. Twenty-one patients had menorrhagia; 15, meno-metrorrhagia; and 9, polymenorrhea. The duration of symptoms, before the institution of treatment, varied from two months to ten years, the majority having had symptoms for more than nine months.

In the group of patients with uterine fibroids, the ages varied from 38 to 50 years. In 7, the bleeding consisted of menorrhagia; in 6, meno- and metrorrhagia; and, in 2, menorrhagia with polymenorrhea.

METHODS

Previous studies with testosterone propionate in women have demonstrated that this hormone, if given in adequate amounts, produced characteristic changes in the endometrium[21, 25, 40, 63] (suppression of progesterone effect, inhibition of the normal proliferative picture resulting in hypoplasia or atrophy) and regressive changes (evidence of estrogen deficiency) in the vaginal smear.[55, 63, 64] For this reason, the endometrial biopsy and the vaginal smear serve as useful objective indicators of the activity of the administered hormone and were employed in our cases in correlation with the clinical results. Smears were taken twice weekly, prepared, and

stained as previously described.[26, 65] A pretreatment endometrial biopsy, by suction curettage, was performed in the majority of patients before periods of bleeding. In our attempt to determine the effect of different doses of the hormone upon the vagina and the endometrium, biopsies were taken, in some cases as frequently as once weekly. In the routine management of a case, however, it is not essential to perform repeated biopsies, inasmuch as one can derive sufficient information, for clinical purposes, from the vaginal smears alone.



Testosterone Propionate

Dosage.—Testosterone propionate* was chosen as the most active androgen available.[48] The dosage was varied widely in the early stages of this study, in order to determine the optimal dosage required to obtain a satisfactory therapeutic effect. We had observed that menstruation can be suppressed in normal cyclical women with 500 mg. or more per month. Further experience revealed that there is a considerable variation in the response of different individuals to comparable doses of testosterone. In this series the total dosage was varied from 75 to 2,150 mg., over periods extending from one to seven months. The testosterone propionate was administered in doses of 5 to 100 mg., in sesame oil (10 to 25 mg. per c.c.), intramuscularly, 2 or 3 times weekly, in the gluteal region.

RESULTS WITH TESTOSTERONE PROPIONATE

Endometrial Studies

Preliminary premenstrual endometrial biopsies were performed in 42 cases. Of these, 4 showed hyperplasia and 4 proliferation; the remainder showed normal secretory patterns (Fig. 1).

Effect of Testosterone on the Endometrium.—As previously reported,[21, 25, 27, 40, 63] testosterone propionate, if administered in doses of 500 mg. or more per month, may reduce the endometrium to a state of atrophy (Fig. 2) or hypoplasia. This is associated with a temporary suppression of menstruation. With smaller doses (approximately 300 to 400 mg. in one month), the corpus luteum effect on the endometrium (secretory phase) alone is suppressed with preservation of the proliferative picture, menstruation usually being delayed a few days and reduced in amount.[63] With still smaller doses (less than 300 mg. per month), premenstrual biopsies after testosterone propionate reveal the presence of a secretory phase, the estrogen and progesterone activity being apparently uninfluenced by the testosterone. It is noteworthy that after the discontinuation of treatment, the normal proliferative (Fig. 3) and secretory patterns (Fig. 4) of the endometrium reappear within two to three months, usually even in cases in which menstruation has been suppressed and the endometrium has been reduced to a state of advanced atrophy.

Effect of Testosterone on the Vaginal Mucous Membrane.—It has been pointed out that in large doses (500 mg. or more per month), testosterone produces striking involutional changes in the vaginal mucous membrane, coinciding with the period of induced amenorrhea.[55, 63, 64] The smears exhibit cytologic changes indicative of varying degrees of estrogen deficiency. In some instances the involutional changes are as striking as in cases of advanced senile atrophy, the vaginal smears consisting

*For the testosterone propionate used in this investigation, we are indebted to Dr. E. Schwenk, Schering Corporation, Bloomfield, N. J. (Oreton), and to Mr. R. C. Mautner, Ciba Pharmaceutical Products, Summit, N. J. (Perandren).

Fig. 1.—Case A. S., aged 32, gravida i, para i, had regular menstrual (28 to 30 days) cycle, menorrhagia (periods lasting nine to twelve days), fourteen months' duration. Preliminary endometrial biopsy (E1) taken two days premenstrually, showing characteristic secretory pattern. Patient was then given 650 mg. of testosterone propionate during the following thirty days.

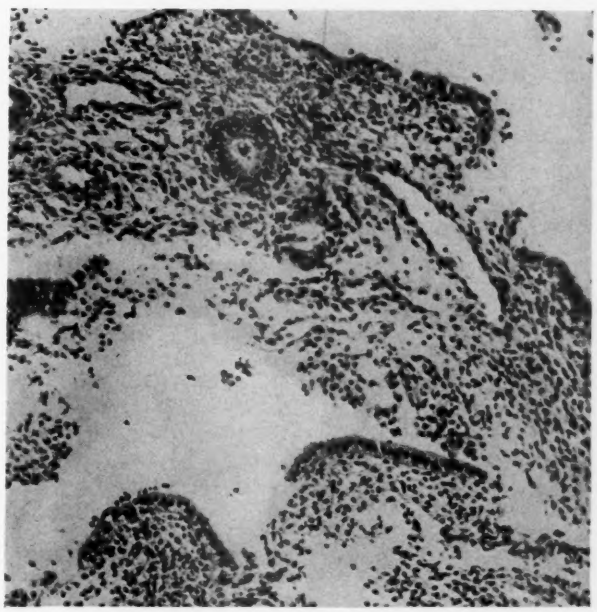


Fig. 2.—Case A. S. Endometrial biopsy (E2) taken thirty-five days after the preliminary biopsy, i.e., five days after the expected date of onset of the next period which failed to appear. The biopsy reveals the endometrium to be in a state of marked involution.

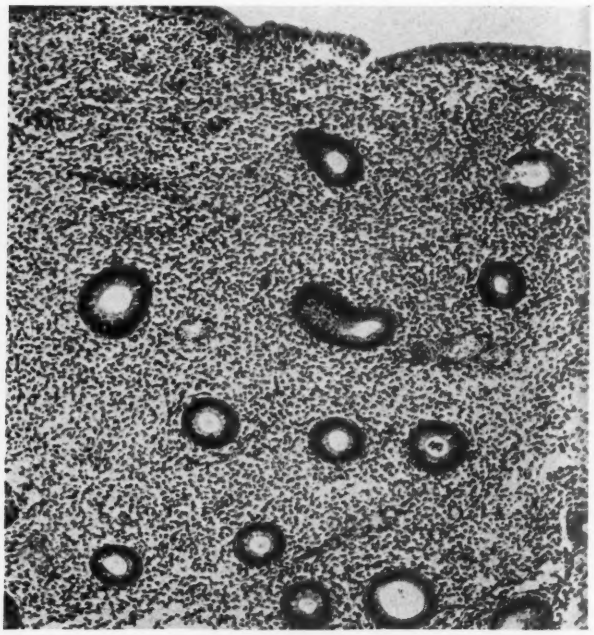


Fig. 3.—Case A. S. Endometrial biopsy (E3) taken sixteen days after the preceding one (Fig. 2), showing moderate proliferation indicative of restoration of estrogen activity.

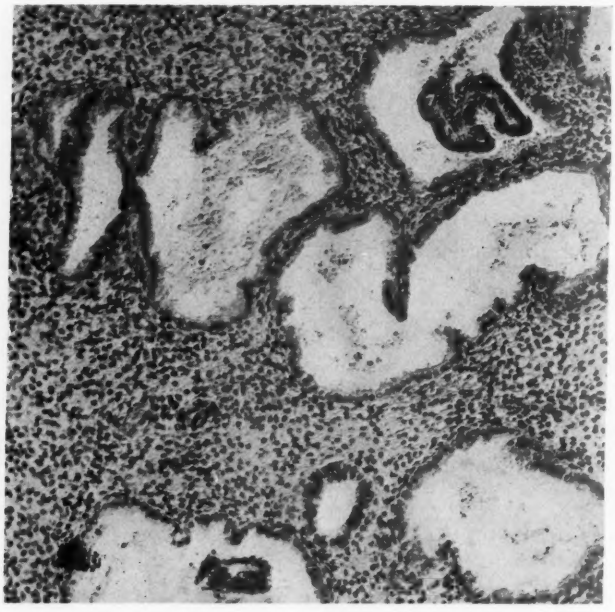


Fig. 4.—Case A. S. Endometrial biopsy (E4), taken two weeks after E3, showing secretory pattern indicative of normal estrogen and progesterone activity. Normal menstruation began three days later.

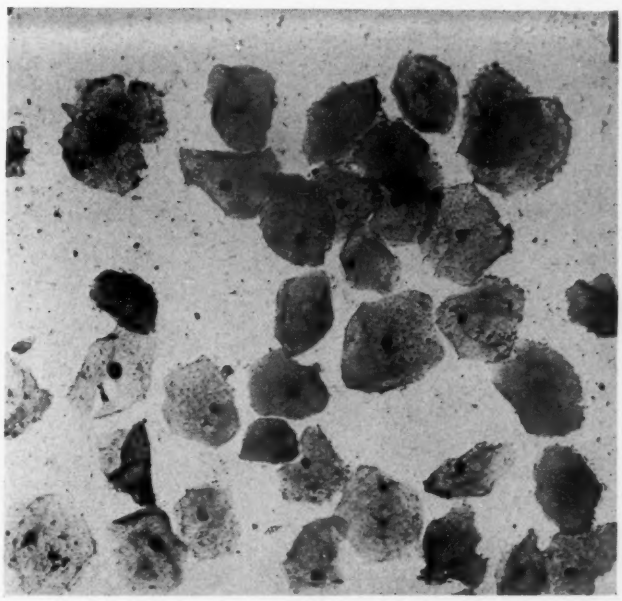


Fig. 5.—Case A. S. Normal pretreatment vaginal smear (V1), showing large, squamous epithelial cells with small, deeply-staining nuclei.

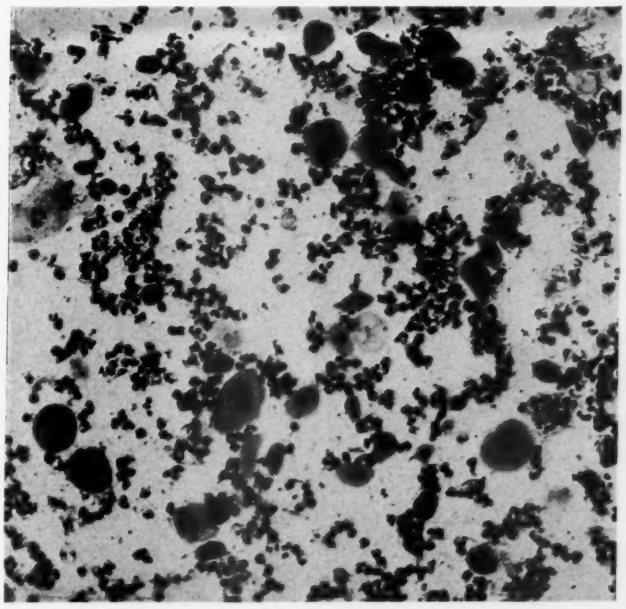


Fig. 6.—Case A. S. Vaginal smear (V2) taken at the same time as E2 (Fig. 2) during period of amenorrhea induced by testosterone propionate. The smear reveals a preponderance of small, round, and oval epithelial cells with prominent nuclei, numerous leucocytes and almost complete absence of the large squamous epithelial cells. The smear resembles the estrogen deficiency smear characteristic of senile atrophy.

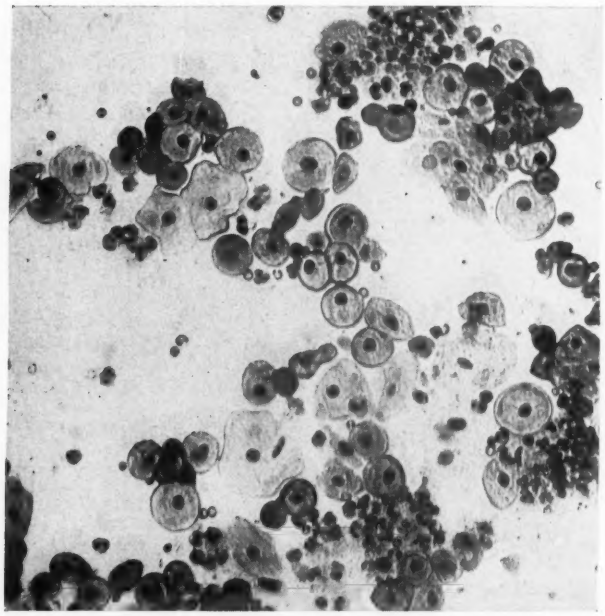


Fig. 7.—Case A. S. Vaginal smear (V3) taken ten days after V2, revealing larger epithelial cells and a decrease in leucocytes, indicating beginning estrogen activity.

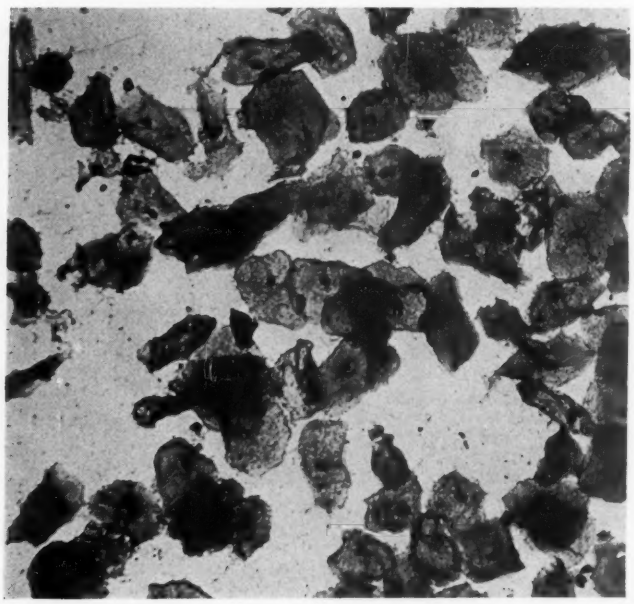


Fig. 8.—Case A. S. Vaginal smear (V4), fifteen days after V3 (which was eight days before the occurrence of menstruation). The smear shows restoration of large, squamous epithelial cells and absence of leucocytes, indicative of normal estrogen activity.

of small, round, and oval epithelial cells with prominent nuclei ("deep cells" of Papanicolaou;[54] "atrophy cells";[26] "estrogen deficiency cells";* and leucocytes) (Figs. 6 and 7). In some cases the androgen effect is less marked, the smears showing only a scattering of the "atrophy cells" among the large squamous epithelial cells.

Our studies have, furthermore, revealed a fairly consistent chronologic relationship between the appearance of regressive changes in the endometrium and vaginal mucosa and the advent of the defeminization phenomena. It was noted that the latter were almost invariably preceded by the signs of morphologic regression in the vaginal mucosa and the endometrium. During the early stages of our studies, we did not fully appreciate the practical importance of this observation. Subsequently, however, it became apparent that by discontinuing the testosterone as soon as the first signs of morphologic regression made their appearance, the masculinization phenomena could be avoided. On correlating the changes in the endometrium, vaginal mucosa and vaginal smears, we found that the smears reflected the early regressive changes as consistently as the endometrial or vaginal biopsies. For this reason, we have employed the vaginal smear as an index of testosterone saturation and consider it an indispensable safeguard in regulating the dosage of testosterone in the treatment of gynecologic conditions.

RESULTS IN 45 CASES OF FUNCTIONAL BLEEDING

Primary Results:	
Temporary amenorrhea	29 cases
Normal menses	15 cases
Slight improvement	1 case
Late Results (Period of Observation 6 to 38 Months):	
Normal menses	26 cases
Hypomenorrhea	3 cases
Amenorrhea (menopause)	1 case
Moderate improvement	12 cases
Failures	3 cases

CLINICAL RESULTS

Control of excessive bleeding in the functional group occurred during, or soon after, treatment, in all but one case. Good primary results occurred, therefore, in 97.7 per cent of the cases. In many instances, improvement became apparent after one month; in others, only after two or three months of treatment. In 29 cases, a temporary amenorrhea of one and one-half to four months was first established, followed by normal menses. In 26 cases a normal menstrual cycle was established and persisted during the entire period of observation which, in several cases, extended up to thirty-six months. In 5 of this group, moderate menorrhagia returned several months after the discontinuation of the treatment. These patients were controlled with supplementary courses of testosterone for one or two months, the monthly dosage varying from 100 to 200 mg. In 3 cases, there was complete recurrence of the menorrhagia after intervals of six, eighteen, and twenty months' duration, respectively. One woman, 50 years of age, developed amenorrhea and menopausal symptoms. Three others, also in the fifth decade of life, showed alternating periods of hypomenorrhea and amenorrhea. In 12, the bleeding, though not restored to normal, was considerably diminished in amount and duration. Thus, after a follow-up extending up to thirty-six months, satisfactory results persisted in 66.6 per cent of the cases and moderate improvement in 26.6 per cent. The remaining 6.8 per cent of the cases were considered therapeutic failures.

*We have suggested calling these cells "atrophy" or "estrogen deficiency" cells, since their presence in the smear is the result of some degree of atrophy of the vaginal mucous membrane and is indicative of a state of estrogen deficiency.

RESULTS IN 15 CASES OF MENO-METRORRHAGIA ASSOCIATED WITH FIBROIDS

Primary Results:		
Temporary amenorrhea	4 cases	
Normal menses	9 cases	
Moderate improvement	2 cases	
Late Results:		
Normal menses	6 cases	
Moderate improvement	2 cases	
Failures	7 cases	(submucous fibroids)

CLINICAL RESULTS

The results in the series of cases with uterine fibroids were not as satisfactory. The immediate results in this series were encouraging. Of 15 patients, 9 had normal, regular menses; 4, amenorrhea; 2, moderate improvement. After discontinuation of treatment, however, only 6 remained normal and regular; 2 showed approximately 50 per cent improvement; 7 had complete recurrences. Five of these patients with failures were subsequently operated upon because of the persistence of the bleeding. All were found to have submucous fibroids which probably accounted for their failure to respond to testosterone. It is worthy of note that we failed to detect in these cases any appreciable shrinkage in the size of the fibroids as a result of the treatment with testosterone.

The primary result in the case of adenomyosis of the uterus was good while the patient was receiving the testosterone. However, there was a complete recurrence of symptoms two months after the discontinuation of treatment, and hysterectomy was subsequently performed.

"ARRHENOMIMETIC" EFFECTS

Thirteen of the 61 patients in this series exhibited side-effects that are worthy of note. A number developed masculinization (arrhenomimetic) phenomena, viz., slight hirsuties of the face and extremities (5 cases), deepening of the voice (6 cases), and enlargement of the clitoris (3 cases). In 5 instances, slight acne appeared on the chest, back, and face. A few patients developed all 3 symptoms, i.e., hoarseness, hirsuties, and acne. With but one exception, *none of these complications occurred in the patients receiving less than 500 mg.* The exception was a patient who developed slight acne and hirsuties after 315 mg.

The hirsuties occurred only in brunettes, 3 of whom had had slight hirsuties before. It is interesting to note in this connection that Hamblen[28] has reported that brunettes excrete more androgens than blondes. The greater susceptibility of brunettes to testosterone may be related to this fact. It is worthy of note that a number of patients who received very large doses (up to 2,000 mg.) of testosterone, sufficient in many cases to suppress menstruation, did not develop any of these symptoms. The androgen effects began to regress several weeks after discontinuation of treatment, and in all but 2 cases disappeared after six months. In these two, some hoarseness and slight facial hirsuties have persisted for twelve months, but appear to be diminishing steadily up to the present writing. Both of these patients had received large doses (upwards of 1,500 mg.) of testosterone propionate.

Estrogen Deficiency Symptoms.—Several patients complained of vaginal discharge and vaginal burning during or following the testosterone administration, caused by temporary atrophic changes in the vaginal mucosa. Smears in these cases revealed morphologic changes similar to those observed in postmenopausal vaginitis. The vaginitis is probably attributable to the loss of glycogen from the vaginal mucosa.[64] These symptoms subsided rapidly after discontinuation of the testosterone propionate.

Constitutional Effects.—The majority of the patients volunteered the information that they felt more vigorous, had improved appetite and gained in weight while receiving the injections. A number of the patients, of their own volition, reported a striking increase in libido during the period of treatment.

Effect of Testosterone Propionate on Associated Dysmenorrhea, Premenstrual Tension and Mastalgia.—A number of patients who had dysmenorrhea, premenstrual tension, and premenstrual mastalgia, associated with menorrhagia, reported either considerable improvement or complete relief.

MANAGEMENT OF A CASE OF MENO- AND METRORRHAGIA WITH TESTOSTERONE PROPIONATE

During the experimental stage of our investigation, the dosage of testosterone propionate was varied widely in order to reveal the range of its biologic and therapeutic effects. Accordingly, we have been able to study the clinical, as well as the morphologic, results of doses varying from 45 to 1,000 mg. per month. It soon became apparent that in order to attain a therapeutic effect, it was not necessary to resort to the high doses. Whereas, in the cases in which marked inhibition of the endometrium and temporary suppression of menstruation were induced, good results were achieved, it is significant that comparably good results were obtained in other patients with doses insufficient to suppress menstruation or to produce morphologic evidence of estrogen deficiency in the endometrium and vaginal mucosa. There is undoubtedly a considerable variation in the responsiveness of different individuals to similar amounts of testosterone propionate. This is probably due to variation in the androgen requirements of different individuals.

Until we are able to determine, quantitatively, the androgen needs of the patient, and, in the absence of methods of estimating, individual susceptibility, we deem it advisable to adhere to certain more or less arbitrary limitations of dosage. Each patient must, furthermore, be considered in the light of an individual experiment. It may be necessary to increase or decrease the amount administered, depending upon the response of the patient. Endometrial biopsies and vaginal smears (both of which are office procedures) are of considerable aid in the regulation of the dosage.

Severe Meno- and Metrorrhagia.—For patients with marked bleeding, we suggest 300 mg. per month as the optimal dose, given in single intramuscular injections of 25 mg., 3 times weekly. Vaginal smears should be taken twice weekly and, at the first sign of regressive changes, therapy should be discontinued. If there is no, or only slight, symptomatic improvement during the next menstrual period, a similar course of testosterone should be repeated the following month. If the first menstrual period is moderately improved, 150 mg. in divided doses may be given the following month. If the bleeding is reduced to approximately normal after the first course, a second course should be given the following month, reducing the monthly dose to 100 mg.

Moderate Meno- and Metrorrhagia.—For patients with moderate degrees of menorrhagia or menometrorrhagia, 150 to 200 mg., in divided doses, for the first month, is usually adequate. It is advisable to supplement the first month's treatment with a second course the following month, using approximately half of the first monthly dose.

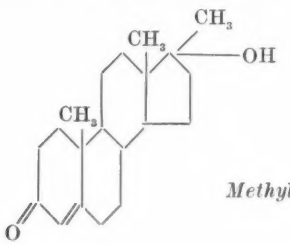
Patients that have shown a tendency to recurrence after an interval of normal menses for several months have been satisfactorily controlled with small doses, e.g., 10 mg., twice or three times weekly, or 25 mg. once weekly, given for four to six weeks.

If menstruation is suppressed or delayed, the further management of the case is determined by the endometrial biopsy and vaginal smear findings. If the endometrial biopsy reveals absence of secretory phase of regression of the proliferative phenomena and/or the vaginal smear shows estrogen deficiency changes, no more testosterone should be given. If at any time during the course of treatment facial hirsuties or coarsening of the voice should occur, therapy should be discontinued. Should acne occur, it need not be considered a serious deterrant to further therapy, since it subsides rapidly after stopping the testosterone. We have found it helpful to use an ointment containing estrogens, locally, in these cases (360 R.U. of estradiol per gram of lanolin base). The vaginitis that may occasionally occur can be readily controlled with vaginal estrogen suppositories (2,500 R.U. of estradiol [progynon DH] per suppository) used nightly for several nights.

RECENT ADVANCES IN ANDROGEN THERAPY

Although the clinical results obtained with testosterone propionate in the treatment of functional bleeding have been satisfactory, the treatment has two objectionable features. These are: (1) the necessity for repeated injections, and (2) the risk of inducing arrhenomimetic phenomena.

Oral Administration of Androgens.—In an attempt to overcome the first of these, we have resorted to two other methods of administering androgens, i.e., by the oral route and by implantation of pellets of the hormone. Testosterone and testosterone propionate are absorbed in such small amounts from the intestinal tract that enormous doses would have to be administered in order to be effective. The expense to the patient would be so great as to make it impractical.

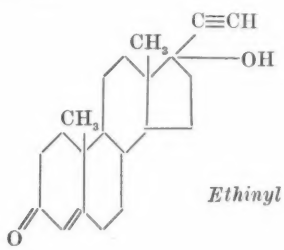


Methyl Testosterone

Methyl testosterone,[20, 58] however, is absorbed much more readily from the intestinal tract. In a study of the biologic properties of this compound, we have found that when administered enterally its effects are very similar to those produced by testosterone propionate given parenterally.[35] Its androgenic potency in women (when given by mouth) appears to be approximately one-third that of testosterone propionate administered intramuscularly. Although our clinical studies with this compound have not been extensive enough to warrant final conclusions, we have sufficient data to lead us to believe that this compound should prove valuable as a therapeutic androgen.

Buccal Absorption of Testosterone in Propylene Glycol Solution.—Recently we have found that testosterone in solution in propylene glycol is absorbed from the sublingual space. Preliminary studies indicate that this may prove to be a simple and economical method of androgen administration.

Implantation of Androgen Pellets.—With the objective in view of eliminating frequent injections, we implanted 22 patients with pellets of testosterone and testosterone propionate.[36] The results of this study are being reported in detail elsewhere. Although some very interesting information was obtained concerning the rate of absorption of the hormone and its effect upon the surrounding tissues, the implantation of testosterone appears to be of little, if any, practical value as a therapeutic procedure in gynecology.



Ethinyl Testosterone

VALUE OF METHYL TESTOSTERONE

In an attempt to find a therapeutic agent that would possess the therapeutic effectiveness of testosterone propionate without its arrhenomimetic properties, we have used a number of androgens of low androgenic potency, viz., androstenedione,

androstenediol and ethinyl testosterone. The first two proved disappointing; the last seemed to possess therapeutic potentialities. This compound (ethinyl testosterone; pregneninolone; $\triangle^4$ pregnenin-20-on-3-ol-17; anhydro-hydroxy-progesterone), which was synthesized by Inhoffen, Longemann and Serini[32] and is structurally very closely related to testosterone and progesterone, has been shown to possess the following biologic properties: (a) a progesterone-like action (progestomimetic) in immature rabbits (being active when administered orally);[33, 59] (b) an estrogen-like action (estromimetic) on the uterus and vagina of adult and immature rats;[17, 66] and (c) an androgen-like action (andromimetic) in capons and rats.[13, 17, 66]

In human beings, this compound has been shown to produce a progestational effect on the estrogen-primed endometrium;[10, 67] to be very weakly estromimetic and to exhibit no arrhenomimetic properties.[68] There have been but few reports of the clinical use of this compound. Zondek and Rozin[74, 75] have reported induction of uterine bleeding with pregneninolone; Hamblen[29] has investigated its value in the treatment of functional uterine bleeding with equivocal results. We have used this compound for a period of eighteen months in both functional meno- and metrorrhagia[22] and dysmenorrhea.[35, 69] Although the dysmenorrhea was relieved in a number of patients, pregneninolone appeared to have no significant effect on the abnormal bleeding.

DISCUSSION

A number of questions arise with regard to the use of testosterone in the treatment of abnormal bleeding, questions relating to (a) its efficacy as a therapeutic agent; (b) the undesirable effects that may result from its use; (c) the modus operandi; and, as a corollary to the last, (d) the theoretical implications as to the role played by androgens in the causation of normal and abnormal uterine bleeding.

Therapeutic Efficacy.—It is apparent from the results reported here that very satisfactory results can be obtained with testosterone propionate in the treatment of some types of functional uterine bleeding. The persistence, furthermore, in the majority of the cases, of a normal menstrual cycle for many months after discontinuation of the treatment, prompts us to recommend testosterone propionate as a very effective and satisfactory therapeutic agent in the treatment of functional uterine bleeding.

In contrast to the high percentage of good results obtained in the functional group, comparatively poor results were noted in the patients in whom bleeding was associated with fibroids. The initial results in the group with fibroids were quite good. However, after the discontinuation of testosterone, menstruation remained normal in only 6 of the 15 patients. In 6 patients, the abnormal bleeding recurred completely. Four of these were subsequently operated upon and found to have submucous fibroids.

Are we to attribute the failure in these cases to the presence of the submucous fibroids? It is, of course, unsatisfactory to draw conclusions from so small a number of cases, but, based on the results of this series, the conclusion seems warranted that when abnormal uterine bleeding is associated with submucous myomas, testosterone is not likely to have more than a temporary effect.

As regards the patients with small fibroids in whom abnormal bleeding was completely controlled, it is an open question whether the excessive bleeding was attributable to the small fibroids or to the same etiologic factors which cause excessive bleeding in the functional group.

In any event, it appears from these studies that menorrhagia and menometrorrhagia, associated with submucous fibroids, are not satisfactorily controlled by testosterone, whereas, in the presence of small or intramural fibroids, the results are likely to be as satisfactory as in the purely functional group.

Undesirable Effects.—Under this caption are included masculinization (arrhenomimetic) phenomena and the estrogen deficiency symptoms which result from large doses of testosterone. As has been pointed out above, this syndrome, viz., the amenorrhea, hirsuties, hoarseness, and enlargement of the clitoris, is induced when doses of 500 mg. or more per month are administered. The therapeutic dose is considerably smaller and, with the exception of an occasional susceptible case, produces none of these complications. It is, furthermore, possible to avoid these phenomena, even in the susceptible cases, by paying close attention to the cytologic changes in the vaginal smear. At the first sign of androgen effect, the testosterone should be discontinued. If this safeguard is employed, the valuable therapeutic properties of testosterone can be utilized without fear of inducing any of the undesirable arrhenomimetic phenomena.

Relationship to Fertility.—The question may be raised whether testosterone may interfere with fertility. It is logical to assume that when sufficient testosterone propionate is given to abolish the progesterone effect in the endometrium and to suppress menstruation, ovulation has probably been inhibited. Furthermore, histologic studies[24] of the ovaries of women, with normal ovulatory cycles, who had been injected with large doses of testosterone propionate, indicated that maturation of the follicle and ovulation are inhibited. It is worthy of note that excretion of pregnanediol was suppressed during the current cycle in these cases.[34] The regular reappearance of the secretory phase in subsequent cycles indicates, in the light of our present knowledge, the resumption of the normal gonadotropic activity by the pituitary and restoration of normal follicle growth and ovulation with its attendant hormone production. In one case, following the administration of large doses of testosterone propionate (sufficient to suppress menstruation and induce characteristic regressive vaginal smear changes), conception took place during the period of amenorrhea and within two weeks after the return of the smear to its normal (follicular) status. This patient was delivered of a normal child nine months later and, during the succeeding twenty-four months, has had normal regular cycles. There have been 2 other normal pregnancies in this series. Mazer and Mazer[46] reported 4 pregnancies following testosterone therapy. Of these, one patient had an induced abortion, and 3 were delivered of normal infants.

Modus Operandi of Testosterone Propionate.—The hormonal mechanisms involved in normal, as well as in abnormal, uterine bleeding are still but incompletely understood. Any discussion, therefore, of the modus operandi of a therapeutic agent that is presumed to control abnormal uterine bleeding must be regarded as highly speculative. However, a few facts are known and, on the basis of these and our knowledge of the biologic effects of testosterone in women, we are prompted to formulate a theory concerning the mechanism of the testosterone action.

In order to understand the modus operandi of testosterone propionate, it is essential that we define, as clearly as possible, the factors that are involved in uterine bleeding, whether normal or abnormal. We can refer but briefly here to the established facts and generally accepted views. For comprehensive accounts of the experimental studies and theories relating to menstruation, the reader is referred to the reviews of Allen,[3] Corner,[11] Bartelmez,[4] Markee,[41] Engle,[18] and Ehrenfest.[16] It is the consensus among workers in the field that uterine bleeding occurs whenever there is a withdrawal of estrogens or progesterone. The studies of Bartelmez,[4, 5] Markee,[41-44] Daron[14] and others have shown that the blood vessels of the endometrium are under control of the ovarian hormones. During the latter half of the cycle, the "spiral arteries" undergo rapid growth and become more strikingly coiled.[14] After withdrawal of the growth stimulus a series of vascular changes occur which culminate in endometrial desquamation and menstrual bleeding. In spite of these ingenious and elaborate studies, we have very little information about the aspect of menstruation which is of paramount importance to the clinician, viz., *the factors that control the amount and duration of the bleeding.*

Our studies, as well as those of others, have shown that excessive bleeding may occur from an endometrium showing normal proliferation, a typical secretory pattern or hyperplasia. The abnormal bleeding, therefore, cannot be attributed to, or correlated with, any specific deviation from the normal endometrial pattern. Evidence is accumulating which seems to indicate that the importance of the endometrium, per se, has been overstressed in regard to abnormal bleeding and that the role of the endometrium may be purely a passive one. However, it is worthy of note that in all of the cases of abnormal bleeding, regardless of the type of endometrial pattern found, the endometria all indicate the presence of one factor common to all,* a factor which is apparently indispensable for uterine bleeding, whether normal or abnormal, viz., estrogen stimulation. And although the experimental studies in monkeys and human beings indicate that *withdrawal* of gynecogens initiates bleeding, it has also been our experience that, in women, bleeding may begin *during the course of estrogen administration*, providing the estrogen stimulation is sufficiently intense and maintained for an adequate length of time. Furthermore, we have reason to believe that bleeding may be prolonged by continued estrogen stimulation. Thus in patients implanted with estradiol crystals (in whom estrogen stimulation was maintained for many months), we have found evidence of active endometrial proliferation or hyperplasia even after a fourteen-day period of profuse bleeding.

It has been shown that if testosterone propionate is given in sufficient doses to women it can completely nullify the action of the estrogens and the other hormonal factors that are responsible for the initiation and continuation of bleeding, leading to suppression of menstruation and hypoplasia or atrophy of the endometrium. There is reason to believe that this effect is achieved through a combination of 3 actions, viz., (a) inhibition

*The exceptions to this are the comparatively uncommon instances of bleeding from an atrophic endometrium ("senile endometritis").

of the gonadotropic activity of the hypophysis which results in suppression of ovulation and estrogen formation; (b) inactivation of the estrogens (or nullification of their biologic effects); and (c) inhibition of the proliferative capacity of the endometrium. Keeping these facts in mind, it is not difficult to explain the control of menorrhagia by massive doses of testosterone. The hypophysis is inhibited so that no gonadotropic hormone is secreted, estrogen production by the ovary is suppressed and, as a result of the rapidly developing deficiency in estrogens, and possibly also because of a direct inhibitory action of testosterone on the uterus, the normal proliferative changes are halted and involutional changes set in. Amenorrhea of variable duration ensues. When the testosterone propionate is stopped, its effects wear off gradually. The pituitary then resumes the secretion of gonadotropic hormones. The ovary responds with ovulation and estrogen and progesterone formation. The endometrium reacts to stimulation by estrogens and progesterone, creating a normal proliferative and secretory pattern which is ultimately shed, resulting in a normal amount of menstrual bleeding.

But how is one to account for the good therapeutic results obtained with small doses which do not suppress menstruation and do not produce the regressive changes in the endometrium? We must assume that, when administered in small doses, testosterone propionate produces a qualitatively similar, though less profound, effect. It is not difficult to conceive that testosterone may only partially inhibit, modify, or "mute" the factors which are involved in the causation of bleeding, and thus establish a normal bleeding cycle without completely suppressing estrogen formation or producing the marked involutional changes in the endometrium. It is true that in a number of our successfully treated patients a period of amenorrhea was first induced, and we cannot deny the possibility that the profound inhibitory effect of testosterone upon the pituitary, ovary, and endometrium may have been the cause for the subsequent establishment of the normal cycle. On the other hand, it should be pointed out that, in a number of cases, the same therapeutic effect was achieved with small doses, without inducing any of the demonstrable inhibitory effects. In any event, the conclusion seems warranted, in the light of our studies, that following the administration of testosterone, a readjustment occurs in the steroid sex hormone organization, which results in the establishment of a normal pituitary-ovarian-uterine relationship. And, as a result of this new order, normal cyclic uterine bleeding occurs. Recently, it has been suggested that testosterone propionate exerts its therapeutic effect through a two-fold action on the uterine musculature, causing "inhibition of the intermittent uterine contractions and a direct stimulative action upon the myometrial elements."[71, 71] The basis for the "stimulative action" on the myometrium is the uterine hypertrophy induced in rats with testosterone propionate by Korenchevsky[39] and his co-workers. Unfortunately, androgens do not induce the same effects in women as they do in rats. Whereas, in rats, testosterone propionate has a stimulating (gynecomimetic) effect on the genital tract, it has an antigynecogenic action in cyclical women.

Physiologic Implications of Androgen Therapy.—The question naturally arises as to whether we are to consider the action of testosterone in the control of abnormal bleeding as a curious therapeutic phenomenon or as a form of physiologic substitution therapy, correcting a qualitative or quantitative androgen inadequacy. If we assume the latter, then, by implication, we automatically assign an essential role to androgens in the hormonal regulation of normal menstruation. Thus Koch and his co-workers[23, 37] have shown that normal adult women excrete significant amounts of androgens (an average of 26 international units of androgens per day, as compared with an average of 40 units per day by males), whereas, before puberty the androgen excretion by girls is extremely small (from 1.8 to 2 international units per liter). It has also been shown that androgens excreted by women are chemically identical with those excreted by males.[9, 75]

As to the function androgens may perform in the complex steroid sex hormone system of women, one must look to the biologic properties displayed by testosterone when it is administered to the cyclical human female. Our studies appear to indicate that, depending upon the dose administered, testosterone propionate tends either to modify or nullify the action of the gynecogenic hormones. And, on the basis of these observations, it is concluded that the endogenous androgens of the human female perform a function which is analogous to the action of exogenous androgens (testosterone propionate). The androgens and gynecogens are thus pictured as being normally in a state of dynamic balance. If the equilibrium is upset in favor of the gynecogens, the resulting imbalance would give rise to dysmenorrhea, menorrhagia, or premenstrual tension; if in favor of the androgens, to oligomenorrhea, amenorrhea, and hirsuties.

SUMMARY AND CONCLUSIONS

1. The results of the treatment of a group of 61 patients with menometrorrhagia with testosterone propionate are presented.

2. The series consists of 45 cases of functional bleeding, 15 cases of menometrorrhagia associated with uterine fibroids, and one case of adenomyosis of the uterus.

3. The effects of different doses of testosterone propionate upon menstruation, the endometrium and vaginal mucous membrane are described.

4. Good primary therapeutic results were obtained in 97.7 per cent of the cases of functional bleeding. Apparent cures (follow-up varying from three to thirty-two months) were obtained in 66.6 per cent; moderate improvement in 26.6 per cent; and failure in 6.8 per cent of the cases.

5. The results in the patients with uterine fibroids were not satisfactory. Although the primary results were good in 87 per cent, symptoms recurred after discontinuation of treatment in 60 per cent of the cases.

6. A preliminary report is made of the results obtained with implants of crystals and pellets of testosterone and testosterone propionate. The therapeutic results were unsatisfactory.

7. The use of testosterone propionate is recommended in the treatment of menorrhagia or menometrorrhagia of "functional" origin, or if associated with small intramural myomas. The results from testosterone propionate are likely to be unsatisfactory if the abnormal bleeding is associated with submucous myomas.

8. The one case of menorrhagia associated with adenomyosis of the uterus was controlled while under treatment, but experienced a complete recurrence of the excessive bleeding after the testosterone propionate was discontinued.

9. The signs and symptoms of testosterone propionate overdosage are described in detail.

10. The importance of studying the cytologic changes in the vaginal smears as a method of regulating the dosage is stressed.

11. A preliminary report on the use of methyl testosterone, ethinyl testosterone, and androgen implantation is presented.

12. A theory is formulated regarding (a) the modus operandi of testosterone propionate in controlling abnormal uterine bleeding and (b) the physiologic role of androgens in the normal steroid sex hormone balance of the human female.

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A CLINICAL STUDY OF ESTROGENIC THERAPY WITH PELLET IMPLANTATION

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THE value of estrogenic substitution therapy in the treatment of menopausal disorders is now well established. Heretofore, this has been accomplished by means of intramuscular injection, oral administration, and local application. In 1937, Deanesly and Parkes[1] studied a new method of administration of the hormone. They implanted subcutaneously highly compressed tablets of crystalline estrone in laboratory animals. They believed that by this method a continuous supply of the hormone could be released in the body, thus simulating the normal physiologic mechanism. They observed that the prolonged action was associated with increased effectiveness of the hormone per unit weight which was perhaps explained by more complete utilization (decreased waste). A year later the same authors[2] in another series of animal experiments studied the absorption rate of the implanted tablets and determined the quantity of hormone used per month by reweighing the implanted tablets at the termination of the experiment. The effects of this long-continued action were in most respects similar to those described by other authors as resulting from the repeated injections of estrogens and the resulting inhibition of formation of the gonadotropic and growth-promoting hormones of the anterior pituitary. As a result of these animal experiments, they suggested that the method would be useful in the treatment of conditions requiring a long-continued and uninterrupted estrogenic effect.

Clinicians began to apply this new mode of therapy to the treatment of the menopausal syndrome. P. M. Bishop[3] found that the implantation of 14 mg. of estrone in the abdominal wall in a menopausal woman caused a marked decrease in the number of hot flushes within a period of one week; an effect maintained for approximately a month. The calculated daily absorption was 0.5 mg. or 5000 I.U.

Salmon, Water, and Geist[4] described a technique of implantation in the gluteal region, and noted complete relief with substitution therapy of 4 to 7 mg. of crystalline estradiol benzoate. They concluded that 25 to 50 mg. should maintain a patient symptom free for many months and suggested that it be given prophylactically to patients following x-ray or surgical castration. MacBryde and others[5] implanted 100 mg. of stilbestrol pellets in the lumbar region and were able to show endometrial proliferation in seven days.

Bennet, Biskind, and Mark[6] reported a series of 21 menopausal patients who received compressed tablets of theelin. These pellets, 3 to 10 in number, weighing 5 to 16 mg., were loaded in a hollow 12-gauge needle and implanted by pressure with a stylet. Biopsies of the vaginal mucosa showed increased proliferation two weeks after treatment. All patients improved under treatment. Symptoms returned gradually and were relieved by second implantation. They noted no infection, inflammation, or abnormal uterine bleeding.

During the past year we have studied the effects of implantation of a single pellet of crystalline estrogens 45 to 65 mg. in weight, in a series of 28 cases. The technique employed was simple and is briefly described as follows: The site chosen for implantation was the region of the groin just above Poupart's ligament. Under ½ per cent novocaine anesthesia, a small incision was made in the skin to allow the introduction of a small curved hemostatic forceps. A channel was made in the subcutaneous tissue and the hemostat withdrawn. The pellet was then introduced a few centimeters laterally to the line of the incised wound. The edges of the incision were then strapped together with sterile adhesive. No sutures were ever used. The patients did not complain of any adverse symptoms and the area healed by primary union within forty-eight hours. The procedure was simple and took but a few seconds longer than an intramuscular injection.

The cases chosen for this study were for the most part those with well-defined symptoms associated with the menopause. These, in turn, were subdivided into the following groups: namely, surgical and irradiation castration, and spontaneous menopause. The common symptoms of menopause, such as hot flushes, sweats, headaches, joint pains, nervousness, irritability, pruritus vulvae, and dyspareunia, were noted at the time of implantation. Vaginal smears, and in some instances, endometrial biopsies were taken during the period of observation. It was found that a week or ten days elapsed in most of the cases before any relief was noted by the patient. In no instance did any abnormal bleeding occur. No evidence of infection, inflammation, or foreign body reaction was observed.

A group of patients with primary amenorrhea were treated by implantation with estrogen pellets. The effect upon development of the secondary sex characteristics and growth in the size of the uterus were noted. It was found that in patients with complete lack of breast de-

velopment, a remarkable increase in size of both the nipple and mammary gland was observed in a comparatively short period of time, i.e., five to six weeks.

Several patients with secondary amenorrhea of long standing were treated with estrogen pellets, and the effect upon the menstrual cycle and the size of the uterus were noted. In this group, the patients did not experience any change in their symptoms unless the secondary amenorrhea was associated with signs of early menopause. The cases are briefly described as follows:

GROUP I. SURGICAL AND IRRADIATION MENOPAUSE

C. R., aged 32 years, had a panhysterectomy in 1939. She had hot flushes, 10 to 15 daily, severe headaches, nervous irritability, and loss of appetite. *Previous therapy:* estrone 20,000 I.U. every week for two months. There was moderate improvement. *Implant:* June 22, 1940, 56 mg. estrogen. *Smears:* June 22, typical castrate smear. September 14, good estrogenic function. October 19, fair estrogenic function.

Result.—All symptoms disappeared up to Oct. 19, 1940, at which time headaches returned. Complete relief four months.

M. K., aged 40 years, had a hysterectomy in 1938. She had hot flushes and severe itching and burning of vulva and vagina. *Previous therapy:* estrone 10,000 I.U., twice a week at intervals for one year with relief of flushes, but not of pruritus. Estrogenic ointment for six months with relief of burning and itching. *Implant:* Aug. 19, 1940, 63.5 mg. estrogen. *Smears:* Mar. 7, 1940, slight function; Sept. 26, 1940, good estrogenic function.

Result.—Relief of all symptoms to date, four months after implantation. No evidence of pruritus vulvae.

Y. S., aged 40 years, had a hysterectomy in 1937. Hot flushes occurred 6 to 8 times daily. Severe headaches. *Previous therapy:* Estrone 10,000 I.U. twice a week for one year. Moderate relief of flushes. *Implant:* Feb. 27, 1940, 60 mg. estrogen. *Smears:* Feb. 14, 1940, marked decrease estrogenic function; March 12, 1940, good estrogenic function.

Result.—Relief of all flushes. Persistence of headaches. Referred for allergy study after two months' observation.

E. Z., aged 43 years, had a hysterectomy in 1937. Hot flushes occurred 10 to 15 times daily. Severe pruritus vulvae. *Previous therapy:* Estrone 10,000 I.U. once or twice a week from June 29, 1940, to Sept. 7, 1940. Flushes reduced, 2 daily. Pruritus unaffected. *Implant:* Sept. 7, 1940, 53.5 mg. estrogen.

Result.—Complete relief of all symptoms two weeks after implant. Oct. 19, 1940, patient in excellent condition. No flushes or pruritus. Last observed on Dec. 21, 1940, condition excellent.

E. B., aged 40 years, had a bilateral oophorectomy in 1930. Pruritus vulvae. Flushes occurred 6 to 8 times daily. Examination, atrophic vaginitis. *Previous therapy:* Estrone 10,000 I.U. once or twice a week at intervals. Relief of flushes but not of pruritus. *Implant:* June 1, 1940, 64 mg. estrogen.

Result.—Sept. 21, 1940, no flushes. Itching disappeared. Mucous membrane healthy. Oct. 5, 1940, occasional itching and few flushes. Complete relief after four months' treatment.

F. G., aged 42 years, had a hysterectomy in 1930. Hot flushes occurred 10 to 15 times daily. Emotional disturbance. *Previous therapy:* Estrone 10,000 I.U. twice a week from Dec. 30, 1939, to May 1, 1940. Symptoms returned when treatment was stopped. *Implant:* May 1, 1940, 68.8 mg. estrogen. *Smears:* May 1, 1940, 10 per cent function; July 7, 1940, 90 per cent function.

Result.—Complete relief after five and one-half months after implantation. Reimplantation on Nov. 2, 1940, of 62.5 mg. of estrogen.

F. M., aged 28 years, had a panhysterectomy in 1939. Hot flushes occurred 15 to 30 times daily. Psychoneurosis. She was confined in Bellevue Psychopathic Hospital for two weeks. *Previous therapy:* Estrone 10,000 I.U. three times a week. Not satisfactory. *Implant:* April 6, 1940, 52 mg. estrogen.

Result.—One week after implant the flushes were absent. There was relief of all symptoms until Sept. 15, 1940. Return of libido and emotional stability. Gain in weight. Reimplantation on Oct. 5, 1940, of 50 mg. estrogen. On Dec. 14, 1940, she felt and looked well. There have been no flushes or emotional upset.

A. C., aged 53 years, had a hysterectomy in 1936. Hot flushes occurred 8 to 10 times daily. She had pruritus vulvae, nervousness, insomnia, and crying spells. *Previous therapy:* Estrone 10,000 I.U. twice a week for one year. Relief of symptoms. Recurrence after injections were stopped. *Implant:* Aug. 29, 1940, 56 mg. estrogen. *Smears:* Aug. 29, 1940, typical castration smear; Sept. 26, 1940, good estrogenic function.

Result.—Sept. 26, 1940, no flushes, itching, or burning. More energy. Still under observation.

M. B., aged 39 years, had irradiation in 1939 for menorrhagia. Hot flushes occurred 20 to 30 times daily. Severe headaches. *Previous therapy:* Estrone 30,000 to 40,000 I. U. twice a week for six months. No relief. *Implant:* April 6, 1940, 55 mg. estrogen. *Smears:* April 6, 1940, typical castration cells; May 5, 1940, moderate function. *Biopsy:* May 5, 1940, complete atrophy of endometrium.

Result.—May 5, 1940, flushes now 10 daily. Patient did not return for further observation or therapy. Partial improvement, no effect upon endometrium.

M. C., aged 42 years, had postradiation in 1937 for fibromyoma. Severe hot flushes occurred 5 to 10 times daily. Nervousness, irritability, insomnia, dyspareunia were present. *Previous therapy:* Estrone 10,000 I.U. once or twice a week for two years. Moderate but transient relief. *Implant:* June 15, 1940, 50 mg. of estrogen. *Smears:* June 17, 1940, decreased estrogenic function; July 8, 1940, excellent estrogenic function; Sept. 23, 1940, decreased function.

Result.—Complete relief of all symptoms for three months. After September 15, she noticed recurrence of flushes. Reimplanted Sept. 28, 1940, 57 mg. of estrogen. Complete relief of all symptoms when last seen, Dec. 23, 1940.

GROUP II. SPONTANEOUS MENOPAUSE

A. N., aged 40 years, had a spontaneous menopause 1 year previously. Hot flushes occurred from 15 to 20 times daily. She was nervous and had lost weight (18 pounds). *Previous therapy:* 10,000 to 20,000 I.U. estrone per week sporadically with moderate relief. Flushes occurred 5 or 6 times a day. *Implant:* April 18, 1940, 50 mg. of estrogen. *Smears:* April 1, 1940, typical castration smear; Sept. 12, 1940, good estrogenic function.

Result.—Complete relief two weeks following implantation. Duration, 5 months. Reimplantation on Sept. 26, 1940, of 58.5 mg. of estrogen following return of symptoms. Still under observation.

K. L., aged 50 years, had a spontaneous menopause complicated with thyrotoxicosis and hypertension. Blood pressure 230/110 (June 1, 1940). Vertigo, tinnitus, vomiting, hot flushes were present. *Previous therapy:* Thyroidectomy four months before. No estrogenic therapy. *Implant:* June 1, 1940, 57 mg. of estrogen. *Smears:* June 1, 1940, slight estrogenic function; July 2, 1940, excellent estrogenic function; Sept. 2, 1940, good estrogenic function; Sept. 20, 1940, decreased estrogenic function. Basal metabolic rate plus 22 per cent. Blood cholesterol 107 mg. per 100 c.c. of plasma (June 3, 1940).

Result.—Two weeks following implant, symptoms improved. No vertigo, vomiting, or tinnitus. Blood pressure 200/110, on Sept. 26, 1940. Return of symptoms five months later. Reimplantation of 59.5 mg. of estrogen Nov. 7, 1940. Has been able to do all housework and is symptom free up to present time, Dec. 23, 1940.

W. J., aged 48 years, had spontaneous menopause 3 years ago. Hot flushes 6 to 10 times daily. She was nervous, irritable, and had pruritus. *Previous therapy:*

Estrone 10,000 I.U. once or twice a week, and for 2 years had relief from flushes. *Implant:* May 6, 1940, 52 mg. of estrogen. *Smears:* March 18, typical castration cells; June 23, excellent estrogenic function; September 5, good estrogenic function; October 1, return of castration cells.

Fig. 1.—Endometrial biopsy before therapy; nonfunctioning endometrium cystic glands. Dense stroma.

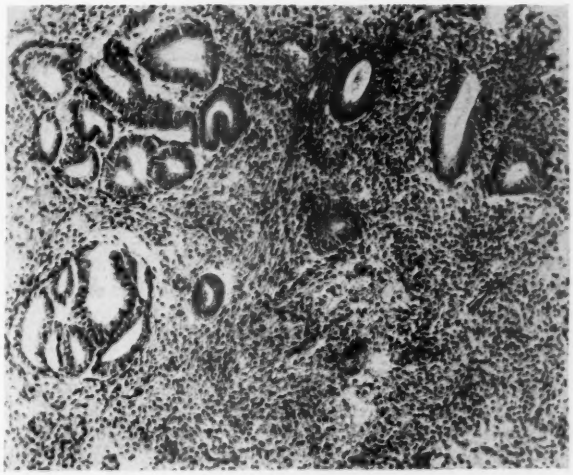

Fig. 2.—Seven weeks after implantation of 55 mg. of estronic pellet. Moderate proliferation of endometrial glands, showing effect of mild estrogenic activity.

Result.—Two weeks after implantation, complete absence of flushes. General feeling of well-being. Duration, four and one-half months. Reimplantation on Oct. 1, 1940, of 56 mg. of estrogen, with alleviation of symptoms one week later. Still under observation.

P. H., aged 53 years, had a spontaneous menopause since June, 1939. Hot flushes occurred 2 to 4 times daily. Nervousness, insomnia, and irritability were present. She had had no previous therapy. *Implant:* April 18, 1940, 50 mg. of estrogen. *Smears:* April 18, marked decrease of ovarian function; May 19, excellent estrogenic function; October 5, decreased function.

Result.—No flushes. General condition much improved for period of six months. Return of symptoms October, 1940. Reimplantation on October 10 of 57.5 mg. of estrogen. Still under observation. Symptom free to date, Dec. 24, 1940.

M. R., aged 35 years, had menopause precox. Her last menstrual period occurred in December, 1935. Hot flushes occurred 3 to 4 times daily. There were malaise and absence of libido. *Previous therapy:* Sporadic treatment with injections of estrone for two years. No effect on general condition. *Implant:* Aug. 15, 1940, 55 mg. of estrogen. *Smears:* August 15, typical castration cells; September 26, very good estrogenic function. *Biopsy:* Oct 11, 1938, atrophic endometrium (Fig. 1). Oct. 3 and 17, 1940, proliferative endometrium (Fig. 2).

Result.—All symptoms were relieved three weeks after implantation. No flushes, return of libido. She was able to do all housework. Three months later, reappearance of symptoms, followed by reimplantation of 60 mg. of estrogen on Nov. 18, 1940. Still under observation.

A. G., aged 47 years, had decreased menstrual periods for two years. She also had severe hot flushes, twitching of eyelids, insomnia, and nervousness. *Previous therapy:* Estrone 10,000 I.U. twice a week. Moderate but transient relief. *Implant:* Aug. 19, 1940, 56.5 mg. of estrogen. *Smears:* October 7, fair estrogenic function.

Result.—Flushes completely disappeared one week after implant. She sleeps better, and is not so nervous. Still under observation four months after implantation.

E. C., aged 45 years, had had scant periods for two years. She also had headaches, hot flushes, 4 to 5 times daily, lack of libido, and was always tired. There had been no previous therapy. *Implant:* Aug. 31, 1940, 46 mg. of estrogen. *Smears:* August 31, poor estrogenic function; September 19, excellent estrogenic function; October 3, excellent estrogenic function.

Result.—Oct. 3, 1940, feels well. There are no flushes or headaches, and she has more energy. There is marked improvement clinically. Still under observation four months after implantation.

D. D., aged 31 years, had menopause precox. She had had irregular periods for one year, every two to three months with one-hour flow. There were severe headaches, hot flushes, and absence of libido. There had been no previous therapy. *Implant:* May 4, 1940, 45 mg. of estrogen. *Smears:* May 4, no estrogenic function; May 18, fair estrogenic function; September 21, decreased function. *Biopsy:* September 21, abortive secretory phase.

Result.—June 15, increased sense of well-being. No flushes or headaches were present. Relief of symptoms for five months.

R. T., aged 27 years, had menopause precox. Hot flushes occurred 20 times daily. She had had amenorrhea for three years. *Previous therapy:* Substitution therapy 10,000 I.U., three times a week, thyroid. *Implant:* Aug. 28, 1940, 38.5 mg. of estrogen. *Biopsy:* Feb. 17, 1940, extreme atrophy.

Result.—Flushes were slight, 2 to 4 times daily, one month after implant. Libido increased. There was relief of symptoms for three months. Flushes reappeared Nov. 23, 1940, but not as severe as before. Reimplantation of 47 mg. of estrogen on November 23.

L. D., aged 32 years, had pruritus vulvae, dyspareunia, atrophy of vulva, and leucoplakia of vulva. *Previous therapy:* Estrogenic ointment for one year at intervals. Moderate relief while under therapy. *Implant:* June 1, 1940, 46.5 mg. of estrogen. *Biopsy:* October 1, nonfunctioning endometrium. *Vaginal biopsy:* parakeratosis.

Result.—Complete relief of all symptoms for four months. Return of itching and soreness Oct. 1, 1940. Leucoplakia of buccal mucous membrane 1 cm. in area anterior to Stenson's duct noticed on Oct. 26, 1940. Itching was worse. Reimplantation of 53.5 mg. of estrogen on Dec. 7, 1940.

GROUP III. PRIMARY AND SECONDARY AMENORRHEA

B. P., aged 23 years, had primary amenorrhea, absence of breast development and pubic hair. There had been no previous therapy. *Implant:* Dec. 5, 1939, 75 mg. of estrogen. *Smears:* December 5, no function; Jan. 15, 1940, excellent function.

Result.—There was noticeable development of both breasts within eight weeks, slight growth of pubic hair, but no menstrual period occurred.

F. S., aged 20 years, had primary amenorrhea. Hypertrichosis. *Previous therapy:* X-ray stimulation of pituitary. Substitution therapy. Infantile uterus on examination. *Implant:* April 6, 1940, 50 mg. of estrogen; Aug. 21, 1940, 57 mg. of estrogen.

Result.—Uterus was slightly larger. There was spotting from September 14 to 17. First real period occurred on October 29 to November 4. Breasts are larger, and the patient feels well.

E. J., aged 30 years, had primary amenorrhea. Hot flushes occurred 6 to 8 times daily. She had dyspareunia, and no breast development. *Previous therapy:* Substitution therapy 10,000 I.U., three times a week. *Implant:* April 28, 1940, 48 mg. of estrogen.

Result.—There had been no flushes six months after pellet implantation. Dyspareunia improved. Patient felt much better with implantation than with injections. Reimplantation of 59 mg. of estrogen Oct. 17, 1940, following return of flushes. Breasts were noticeably larger within eight weeks after implantation, but became smaller four months later.

A. W., aged 29 years, had secondary amenorrhea. Last menstrual period occurred May, 1940. Periods were at prolonged intervals of 6 months. *Examination:* Hypoplasia of uterus. No previous therapy. *Implant:* Aug. 18, 1940, 58 mg. of estrogen. *Biopsy:* September 26 nonfunctioning endometrium.

Result.—Failure. Patient was referred for x-ray therapy to pituitary. (Stimulation.)

B. M., aged 32 years, had secondary amenorrhea. There had been amenorrhea for one year. No previous therapy. No menopausal symptoms. *Implant:* Feb. 24, 1940, 50 mg. of estrogen; Aug. 14, 1940, 51.5 mg. of estrogen. *Smears:* February 24, no function; March 30, excellent function; April 13, moderate function; June 8, fair function; September 12, moderate function. *Biopsies:* February 11, atrophy; March 23, active proliferation; April 6, atrophy; September 11, irregular proliferation; October 4, atrophy.

Result.—Spontaneous period occurred on September 12 for three days, otherwise no change in menses.

A. P., aged 25 years, had secondary amenorrhea for nine and one-half months. There had been loss of libido. *Previous therapy:* Thyroid, and estrone 10,000 I.U. three times a week. *Implant:* Sept. 7, 1940, 55 mg. of estrogen. *Smears:* September 7, fair estrogenic function; September 28, excellent estrogenic function. *Biopsies:* July 24, atrophy; August 28, mild proliferation.

Result.—There was a spontaneous menstrual period on October 18 for four days. She is still under observation. No effect on libido.

DISCUSSION

Group I. Surgical and Irradiation Menopause.—Of the 10 menopause castration cases, 8 patients were relieved of all symptoms one week to ten days following implantation. There was 1 failure in a post-radiation case. One patient was observed only a short period of time and no definite conclusion could be made in this instance. Of the 6 patients kept under observation for a sufficient length of time, it was found that the average symptom-free period was four months. One patient, following radiation therapy, was symptom free for a period of three months. These patients were in a much younger age group than those of the spontaneous menopause. Considering the average dose to be 50 mg. and the average symptom-free period one hundred and twenty days, it would appear clinically that the patients utilized approximately 4,100 I.U. of estrogen per day.

Group II. Spontaneous Menopause.—Twelve patients with spontaneous menopause were treated with pellets, averaging 50 mg. in weight. As in the castration cases, a latent period of one week to ten days elapsed before relief in symptoms was noted by the patients. No abnormal bleeding occurred at any time following the implantation. The duration of the symptom-free period, in those patients observed for a sufficient length of time, averaged five months. This was a longer period than existed in the castration group. Roughly, therefore, from clinical observation alone, we may assume that 50 mg. will last one hundred and fifty days, and the patient absorbs an average amount of 3,000 I.U. per day.

Recently, Corner[7] determined the rate of secretion of estrogenic hormones by the ovaries of the *Macacus rhesus* monkey in an experimental study. He estimated the rate of secretion tentatively as equivalent to 200 I.U. estrone daily. He multiplied this figure by a factor of 15 to allow for the proportionate weight and calculated the rate of production of estrogenic hormone by the human female as equivalent to 3,000 I.U. of estrone daily. There is a striking similarity of the figures obtained by Corner in the production rate of estrone as compared with our clinical estimate of utilization of the hormone in a group of spontaneous menopause cases.

It is interesting to note that those patients who had previous courses of intramuscular injections were able to compare the two forms of therapy. They stated that although intramuscular injections relieved their flushes, intermittently, they did not have the same continuous feeling of well-being, or energy, as when under therapy by pellet implantation. When questioned as to the type of therapy they preferred, they unanimously chose pellet implantation.

It has been the clinical observation of many workers that small amounts of ovarian hormone injected daily give far better results than large amounts administered once or twice a week. This fact was recently brought out by Smith[8] in an analysis of 77 cases of estrogen therapy of the climacteric. It has been his practice to give daily intramuscular injections of 2,000 to 5,000 I.U. of estrone for a period of two or three months in moderately severe cases.

It is a well-known fact that only 15 to 20 per cent of climacteric women require intensive substitution therapy. However, these patients will not submit to long-continued intramuscular injections either daily or every other day. In the usual course of events, as soon as the patient feels better after the first few weeks of therapy, she will become negligent, and the treatment then becomes quite sporadic. Obviously, a method which will afford a continuous flow of hormone over a long period of time, following a single treatment, has tremendous appeal to the patient.

Another clinical observation was made in the pruritus vulvae cases associated with menopause. Some of these patients had previously been treated with estrogenic ointment, both for atrophic and hypertrophic vulvitis. They found that when the ointment was discontinued, their symptoms returned rather promptly and they were much more comfortable for a longer period of time under pellet therapy, especially

in cases of atrophic vulvovaginitis, where long-continued therapy caused increased changes in growth and vascularity of the vaginal mucous membrane. Many patients who complained of frigidity and dyspareunia found that these symptoms were definitely relieved.

Group III. Primary and Secondary Amenorrhea.—In 2 cases of secondary amenorrhea, biopsies showed evidence of a moderate proliferation of the endometrium. Vaginal smears showed an increased amount of cornified epithelial cells. An increase was noted in the size of the uterus which had previously shown evidence of hypoplasia. Implantation had no effect whatsoever upon the menstrual cycle. This observation is, perhaps, consonant with the accepted theory of menstrual bleeding as a deprivation effect. In pellet implantation the effect is continuous, and there are no periods of withdrawal at which times bleeding might be expected.

Three patients with primary amenorrhea were treated with implantation of estrogen pellets, averaging 55 mg. in weight, in order to observe the effect of long-continued administration upon the size of the uterus and upon the development of the secondary sex characteristics. The effect upon breast development in these cases was rather striking. Within a period of five to eight weeks, a noticeable increase in the size of the mammary glands and of the nipple area occurred. Lack of breast development was a disturbing factor in the patient's psyche. This was relieved after development took place in a comparatively short period of time.

CONCLUSIONS

1. Estrogen therapy by implantation of 50 mg. pellets is a safe and effective mode of therapy in cases of menopause.
2. Long-continued administration by implantation is more economical to the patient.
3. Pellet implantation is a simple office procedure.
4. No untoward effects were observed in a series of 28 cases.
5. Therapy by pellet implantation for the menopausal syndrome has proved more effective than that obtained by intramuscular injection.
6. In patients with primary amenorrhea, complaining of lack of breast development, satisfactory results have been obtained with pellet implantation.

The pellets used in this study were composed of the finely powdered estrogenic compounds derived from pregnant mares' urine (estrone, equilin, equilenin, and estradiol). The material was compressed in a steel die punch tablet machine without addition of any inert diluent. Material was furnished through the courtesy of Dr. C. F. Longfellow of G. W. Carnrick Co., Newark, N. J.

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CLINICAL EXPERIMENTS WITH DIETHYLSTILBESTROL*

II. The Treatment of Uterine Bleeding

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THE estrin deprivation theory of menstruation, even though inadequate for the complete understanding of the problem, has been the basis for the treatment of excessive or prolonged uterine bleeding with estrogenic hormone. Such rationale presupposes that uterine bleeding, when present, is a manifestation of relative or absolute ovarian deficiency.

Wintz,[10] as early as 1924, used estrogenic hormones clinically for the treatment of uterine bleeding. He found the method successful in many types of bleeding, including that associated with uterine fibromyomas and abortion. Numerous other reports dealing with the subject have appeared. Those giving special emphasis to the mechanism involved include papers by Goldstine and Fogelson[1] (1931), Siebke[9] (1933), Runge[8] (1934), Martius[5] (1934), Hamblen[2, 3] (1936, 1939), and Karnaky[4] (1940).

I have used diethylstilbestrol in the treatment of uterine bleeding in 31 patients of ages ranging from 12 to 55 years. In a previous paper,[7] I reported the production of artificial menstrual cycles with threshold doses of diethylstilbestrol in women in whom ovarian function was absent. Cyclical treatment was arranged for patients with cyclical uterine bleeding in a similar manner, viz., 1 mg. of diethylstilbestrol per day for seven days, then 5 mg. a day for seven days, followed by 0.3 mg. a day for ten days, or until bleeding recurred. The treatment was started on the third day of bleeding. In most instances bleeding that usually lasted from eight to ten days ceased promptly the first or second day after diethylstilbestrol was started.

If the theory that *relative* ovarian deficiency is an etiologic factor responsible for uterine bleeding is sound, it follows that instances might occur where bleeding would take place in the presence of a high estrin level. In such cases a routine plan of therapy might fail since the dose of 1 mg. of diethylstilbestrol per day might not be sufficient to raise the estrin level above the uterine threshold. When, as it occasionally did, the plan failed, larger doses, up to 15 mg. per day, were used at the outset. The criterion of sufficient dosage was the cessation of bleeding within two days after treatment. When the dose was insufficient there was actually an increase in the amount of bleeding. Subsequent lowering of the dosage to a maintenance level of 1 or 2 mg. a day usually led to an interval free of bleeding for as long as the patient continued to take the drug. Thus in practice it was found advisable to continue the daily administration of diethylstilbestrol for from two to three weeks or until bleeding recurred.

*This study was made possible by the Christine Breon Fund for Medical Research.

RESULTS

Thirty-one patients, ranging in age from 12 to 55 years, complained of uterine bleeding. Classified according to age these patients fell into three groups as follows: (1) menorrhagia of puberty, (2) functional menorrhagia in women of reproductive age, and (3) menopausal bleeding.

Group I.—One patient only, 12 years of age, comprises the first group of menorrhagia of puberty. One cycle of therapy was administered and bleeding ceased promptly the second day of treatment after thirty days of profuse bleeding. The patient has had three subsequent periods which required no further intervention.

Group II.—Ten patients, 21 to 35 years of age, comprise the second group in which the complaint was regularly occurring but profuse and/or prolonged menstrual flow. Seven of these have required but one cycle of therapy. The other three have required 2, 3, and 5 cycles of therapy, respectively.

Group III.—Twenty patients comprise the menopausal bleeding group which consists of individuals whose ages range from 38 to 48 years. In addition to hot flushes, 5 of this group had uterine fibromyomas, 2 had cystic glandular hyperplasia of the endometrium, and in 2 the bleeding had been induced by uncontrolled estrogen therapy. There was no history or other evidence upon examination and endometrial biopsy suggestive of cervical or endometrial malignancy in these patients. Ten of the patients in this group have required but one cycle of stilbestrol therapy. Five have required 2 cycles, 3 have required 3 cycles, and 2 have required 5 cycles of therapy. An additional patient 55 years of age was included in this group because of special interest. Profuse uterine bleeding occurred spontaneously in this individual two months following the implantation of pellets of crystalline α-estradiol.* After twenty days of bleeding she stopped completely the second day of diethylstilbestrol therapy. (The selection of patients for pellet implantation is regularly restricted to patients in whom all pelvic organs have been removed to obviate the occurrence of uterine bleeding. However, in the case cited, the supravaginal hysterectomy performed had apparently failed in the complete removal of reactive endometrium.)

The patients have been so individualized as to their treatment that a table giving data is not practical. Fifty-seven cycles of therapy have been given in which the total dose of diethylstilbestrol ranged from 5 to 94 mg. with an average of 40 mg. per cycle.

Evidence that uterine bleeding actually is a manifestation of ovarian deficiency was demonstrated in most of the patients treated by an abnormally high vaginal pH (5.0 to 7.0) during an interval free from bleeding. This finding was usually associated with a thin, inelastic and atrophic vaginal membrane in the menopausal patients. The lowering of the pH to 4.0 to 4.5 and remission of bleeding followed the administration of diethylstilbestrol. Menopausal women are prone to have menorrhagia associated with other symptoms of failing ovarian function. One of the patients in this series with the diagnosis of cystic glandular hyperplasia of the endometrium has been studied from the standpoint of estrogen excretion in a report dealing with the occurrence of free estrogen associated with uterine bleeding (Palmer[6]). This disease, often referred to clinically as "hyperestrinism," was not associated with excessive urinary estrogen excretion. Urinary hormone assays by numerous observers adequately demonstrate that normal menstruation occurs when the urinary excretion of estrogen is at its lowest level. Such observations are of the kind that give significance to the estrin withdrawal theory of menstruation and support the view that uterine bleeding is a manifestation of a relative "hypoestrinism" rather than "hyperestrinism."

There was no consistency in the duration of the latent interval between the cessation of diethylstilbestrol treatment and the onset of the next uterine bleeding. Sometimes bleeding occurred before the cessation of a course of treatment and in other instances there was no recurrence of bleeding for as long as six or seven weeks. The marked variability in the length of the latent interval between the cessation of stil-

*α-Estradiol was supplied by the Ciba Company.

bestrol therapy and the occurrence of uterine bleeding, as well as the occurrence of bleeding in some instances during therapy, can only be interpreted as reflections of falls in the degree of estrogenic stimulation experienced by the patient. As in the monkey (Zuckerman[11]), it follows that periodical changes occur within the patient of a kind that decreases the effectivity of diethylstilbestrol. When the bleeding did occur and if it was profuse in nature, another cycle of diethylstilbestrol therapy was started. Occasionally the bleeding which followed one cycle of treatment was normal as to amount and duration of flow so that further treatment was unnecessary. In all instances but one the occurrence of bleeding following the first cycle of treatment was less severe than previously.

The experimental data on human beings are not intended to show a superiority of diethylstilbestrol over any of the naturally occurring and other synthetic estrogens. The availability of large amounts of this estrogen, however, makes it possible to demonstrate the efficacy of estrogens in inhibiting uterine bleeding in every instance observed, in a short period of time, with subsequent bleeding of less severity. It appears that unusually large doses as used by Karnaky[4] are unnecessary and in view of the reported toxicity of the drug such large doses should be avoided. Hamblen[2] and Karnaky[4] have reported the same successful results with the use of estradiol benzoate injected intramuscularly. Daily oral therapy, however, for the purpose of maintaining a level of estrogen without the inconvenience and discomfort of intramuscular injections is probably desirable.

Recently ethinyl estradiol* for oral use has been available and already this newest of estrogens shows promise of accomplishing the same desirable effects in the controlling of uterine bleeding. At present, it appears that ethinyl estradiol is effective in smaller doses than are required of diethylstilbestrol.

Nausea and occasional vomiting have occurred in 11 (35 per cent) of the patients under treatment. Details of toxicity studies and disturbed liver function are to be reported elsewhere. Suffice it to say that a reduction of the liver's ability to synthesize hippuric acid (Quick, 1939) has been observed in several patients during treatment with diethylstilbestrol. Recovery of this function appears to be complete in instances where the test has been carried out two weeks after cessation of treatment. Diminished liver function has not been apparent in individuals who have received 1 gram of aminoacetic acid† per day simultaneously with the administration of diethylstilbestrol. The occurrence of nausea and vomiting has not been so troublesome since this material has been used with diethylstilbestrol.

SUMMARY

1. A view is taken that uterine bleeding is symptomatic evidence of that critical state when the uterine threshold to estrogen is above estrin level. Thus normal menstruation or abnormal uterine bleeding is considered to be primarily a manifestation of a relative or absolute ovarian deficiency. This view is supported by the finding of abnormally high

*Ethinyl estradiol was supplied by the Schering Corporation.
†Aminoacetic acid was supplied by the Dow Chemical Company.

vaginal pH values before treatment. Remission of bleeding coincidently with the lowering of the vaginal pH occurred with diethylstilbestrol therapy.

2. Thirty-one patients with abnormal uterine bleeding, ranging in age from 12 to 55 years, were treated with diethylstilbestrol. For the present, the plan adopted for such treatment in young women with functional menorrhagia is 1 mg. of diethylstilbestrol a day for seven days, 5 mg. a day for seven days followed by a decrease in dosage to 0.3 mg. per day for ten days or until bleeding recurs. Such a cycle of therapy is begun on the second or third day of a phase of uterine bleeding or as soon as the patient presents herself if she is bleeding when first seen. For the older women with menopausal bleeding, treatment is begun with a larger dose, 5 to 15 mg. a day until the bleeding ceases. A maintenance dose of 1 or 2 mg. per day is continued for three weeks or until bleeding recurs. Cessation of bleeding is the criterion of sufficient diethylstilbestrol dosage.

3. The existence of a fluctuating uterine threshold to diethylstilbestrol in women with uterine bleeding has been demonstrated. Theoretical as it may be and possibly a manifestation of rhythmical activity on the part of the adrenal or pituitary or both, this factor must nevertheless be taken into account when estrogens are administered to menstruating women. Although this form of therapy may only be temporary in some instances, it has its place as a means of stopping bleeding quickly in cases where other methods of treatment short of hysterectomy have failed. It may be made use of in controlling uterine bleeding preoperatively in cases of fibromyomata uteri.

The diethylstilbestrol used in this investigation was supplied by the Eli Lilly and E. R. Squibb Companies.

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Bayer, R.: Preponderance of Male Fetuses in the Various Months of Pregnancy, Arch. f. Gynäk. **169:** 619, 1939.

The investigations of Bayer lead him to agree with others that there is a preponderance of male fetuses in every month of pregnancy except the eighth. At full term there are 105.6 boys to every 100 girls. However, at the beginning of pregnancy and in the early months, the ratio is 124.2 males to 100 females. Furthermore, there is an increased death rate among the male fetuses in every month except the eighth and including labor. This ratio of fetal deaths is 110.3 males to 100 females. Hence, there is a distinctly higher resistance of female fetuses during intrauterine development.

J. P. Greenhill.

PSYCHOGENIC AND SOMATOGENIC FACTORS IN THE FLUSHES OF THE SURGICAL MENOPAUSE*

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IN NOVEMBER, 1939, observations on certain of the peripheral vascular effects of estrogen in menopausal women were commenced in Greenpoint Hospital. Since it was hoped to obtain objective information on the dermovascular action of the hormone in postmenopausal patients, uncomplicated by psychic factors, it was decided to employ only those who presented themselves at the gynecologic out-patient clinic with a primary complaint of intense and frequent menopausal flushes, and in whom no complicating medical or other predisposing factor was discernible on routine examination.

In accordance with current concepts,[3] it was believed at the outset that the most common symptom of the menopause syndrome after surgical removal of the ovaries, or after x-ray sterilization, is vasomotor instability, usually with the absence of well-marked psychic signs. It was planned, therefore, to use such patients for the most part. By so doing, it was thought that more objective studies could be made. This was particularly desired, since it has been observed recently[4] that whereas vascular disturbances in the menopausal and postmenopausal period respond to estrogen therapy, the neurotic and psychotic aspects of the syndrome are unaffected by the hormone. Consequently, it was a matter of some surprise to observe that in not a small proportion of this group of patients (10 out of 13) in whom artificial menopause had been induced, it was possible to relate relief from the menopausal flushes to specific readjustment of some psychogenic, medical, or social problem. The present report recounts these experiences, resulting from careful study of the patients for periods lasting up to twelve months. It may be well to emphasize that the presence of such factors seldom was revealed in early interviews, but only later when the patients became more talkative and the conditions of the vascularity experiments became less strange.

OBSERVATIONS

Twenty-four patients comprise the group employed in this study. Of these, 6 (3 in natural menopause and 3 in surgical menopause) were eliminated from study

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We are indebted to Dr. Thurston Scott Welton, Chief of the Service on which these studies were made, for the privileges extended to us, and for interest in the progress of the work.

without relief, because they suffered from a variety of conditions that rendered them unsuited to, or uncooperative for, the primary object of our vascular study. These included essential hypertension, proliferative hypertrophic arthritis, acrocyanosis with rachialgia and hypothermia, paranoid conditions and extreme melancholia with undernutrition. Of the remainder, careful and extensive observations have been made. One group (see Table I), consisting of 3 patients in surgical menopause and 4 in natural menopause, was not found to exhibit any particular psychogenic aspect. It is true that 3, in natural climacteric, were somewhat neurotic, but it was found, as Ripley, Shorr and Papanicalaou[4] observed, that prompt and continued relief from menopausal flushes was obtained with estrogen* (supplemented occasionally with phenobarbital) without affecting the melancholia. Of the remainder, there was no doubt in the minds of the observers that at the outset the patients were in much distress from "suffocations" and flushes, and it was equally clear that complete relief was promptly afforded by the hormone. It is possible, of course, that some psychic or other condition of the patient or her environment may have been corrected consciously or unconsciously by her, her family, or her friends, and that this contributed to the relief which we have ascribed primarily to estrogen. If so, we were unable to bring such factors to light.

In the third group of patients (see Table II), there were 8 in surgical menopause, 2 in irradiation menopause, and 1 who experienced intense flushes premenstrually. This patient had menometrorrhagia, and during a period of previous hospitalization her condition had been diagnosed as dementia precox. While the high lights of the several cases will be seen in Table II, the essential features of two of these may be re-emphasized against a more ample statement of the cases. This group of patients, with the exception of the last, have in common the fact that although each lacked productive ovarian tissue, administration of estrogen either did not relieve the flushes substantially, or continuance of the hormone at a high dosage level did not prevent the recurrence of symptoms if some specific disturbing condition became renewed in the course of treatment. This group is of interest, therefore, because it was found that they presented a psychogenic or other condition as a co-factor, with estrogen deficiency, in the genesis of flushes in induced menopause; they were not merely coincidental accompaniments of the menopause syndrome.

In several of these cases, the role of such a co-factor was forced upon us. Thus, one patient (V. L.) was seen in November, 1939. At that time, flushes were not sufficiently frequent or intense to cause her to be "needled." Two weeks later, she appeared at the clinic of her own volition. At this time she was nervous, excitable, and the victim of flushes which came over her one upon another. Estrogen was given in high dosage, and the patient was instructed to return twice weekly. Flushes became less for a day, but returned with only moderate diminution in intensity for ten days. With continued treatment, there appeared to be satisfactory relief from flushes. About the time this point was reached, a freshly healed scar was noted, as her scarf slipped down, just above the manubrium. It was then learned that her husband had attempted to stab her two days before the flushes had become unbearable. The relief which she sought and we ventured to give with estrogen coincided with court procedures during which her husband was put on probation; the flushes disappeared within a day of the time that relative peace in her home was assured. Estrogen was withdrawn for two months, but it was resumed at the end of this time when the patient returned to the clinic with renewal of intense flushes. This time, however, a bruised eye, broken glasses, and a bandaged forehead testified to the source of her trouble. A single injection of a small amount of estrogen was followed by prompt relief, but this coincided with assurance by the court that her assailant, a relative by marriage, would not be permitted to come in the vicinity of her home. The patient has remained almost free of symptoms since that time, except for moderate flushes, not sufficient to require steady treatment, particularly during the summer months when the patient worked as a domestic servant.

*The hormones used were generously supplied by various concerns, as follows: Abbott Laboratories, estrone and estriol; Ciba Pharmaceutical Products, Inc., estradiol, estradiol-dipropionate and testosterone-propionate; Parke, Davis & Co., estrone; Schering Corporation, estradiol, estradiol-benzoate.

TABLE I. PATIENTS EXPERIENCING RELIEF FROM FLUSHES AND SWEATS, PRIMARILY AS A RESULT OF ESTROGEN

NAME	AGE	MENOPAUSAL OR CLIMACTERIC STATE	PSYCHOGENIC OR OTHER CONTRIBUTING FACTOR TO THE SYNDROME	REMARKS CONCERNING TREATMENT, CONDITION AND RESPONSE	RESULT OF TREATMENT
H. F.	54	Surgical, 5 years' duration	Nothing found of a specific nature; seems emotionally unstable	Endocrine obesity; headache, backache, arthritis, kraurosis vulvae. Estrogen with occasional phenobarbital gave relief from flushes and sweats.	Flushes relieved. Arthralgia remained. Discharged after 6 months.
A. N.	42	Surgical, 1 month's duration	Job as cashier made her nervous immediately after operation; never did before; flushes became intense at this time, but began the previous summer	Neat appearance, pleasant disposition, and not introspective. Prompt relief with estrogen. Talked of returning to work after one month, returned to work after treatment for 5 months.	Completely relieved of flushes. Discharged after 6 months.
F. W.	42	Surgical, 3 months' duration	States flushes come day and night; cold at night; no psychogenic factor found in observations lasting 6 months	Flushes, sweats, chills come all the time; headache at times and arthralgia. Prompt relief with estrogen, but slight tendency for recurrence in hot weather.	Prompt relief. Discharged after 6 months.
M. M.	47	Natural, 3 years' duration	No psychogenic factor found, although there was illness in family	Chief complaint, flushes and sweats for over a year. Prompt relief with estrogen; no return when house burned or uterine bleeding returned. Moderate flushes with effort of moving.	Prompt relief. Discharged after 7 months.
H. K.	52	Natural, 2 years' duration	Fears high blood pressure. Somewhat melancholic. Continued to suspect high blood pressure even when assured it was not high	Flushes frequent and severe; dizzy, pounding sensation in head, insomnia. Blood pressure 132/75-70; urine negative. Prompt relief from flushes but other symptoms remained.	Relief from flushes; other symptoms remained. Treatment stopped after 3 months.
S. L.	43	Natural, 15 months' duration	Melancholia; no particular factor noted; relief money inadequate for family	Flushes, sweats, chills; headache; kraurosis vulvae, pruritis; insomnia; very susceptible to heat, and shows marked effort syndrome. Prompt relief from flushes with estrogen; phenobarbital for insomnia.	Relief from flushes. Continuing injections, over 7 months.
N. S.	56	Natural, 10 years' duration	Involutional melancholia with talk of suicide; general debility from undernutrition and diabetes mellitus	Incessant flushes, sweats and chills; insomnia and arthralgia. Estrogen, with phenobarbital periodically, gave much relief.	Relieved of flushes; worries and arthralgia still present. Continuing treatment.

Another case in which relief of flushes was even more certainly ascribable to removal of a neurosis was that of D. T., a negress, 39 years of age. She was formerly married, but now lived with her mother; both gave the impression of being outwardly religious, and read books on character improvement. The patient was, in her own words, "extremely passionate." Her complaint was that of flushes, drenching sweats, trembling, weakness, and headaches. Some days were free of symptoms, but more often were incessantly present. With estrogen, the intensity of the flushes lessened somewhat, but not the frequency. It was then noted that they commenced, on the troubled days, in the early morning hours, and continued thereafter for an indefinite period. Phenobarbital was without effect. About this time (after two and one-half weeks of intensive estrogen therapy), the patient confided the fact that the only relief she could obtain was from repeated masturbation, but this, she had been told by friends, would cause "softening of the brain." The conflict, which had existed long before bilateral ovariectomy and hysterectomy seven months previously, failed in the presence of the ovary to bring on any physiologic changes typical of the menopause syndrome. Soon after the operation, however, the ovarian deficiency was clearly a co-factor in the syndrome. Since the flushes and their attendant sequelae were promptly relieved within four days after the patient was assured that masturbation would not lead to the consequences which she feared, and since estrogen was of little use at the outset, it is clear that the symptomatology of this instance of surgical menopause resulted from *both* hormonic and psychogenic factors.

The extent of, and basis for, relief from menopausal flushes in the remaining cases of this series may be seen in Table II. In each, it is ascribable to correction of a psychogenic factor, and in one (D. M.) this was coupled with periodic nutritional deficiency which dietary care corrected very promptly. The neuroses with which it was necessary to deal ranged from child-parent conflicts of specific sorts (D. M., J. N., E. M., C. O.) and cancerphobia (R. W.) to various types of melancholia, most often attributable to insufficient money or to social maladjustment (M. D., E. M., M. diL., R. W., J. N.). One was clearly a case of insanity (F. B.) in whom appropriate suggestion alleviated the flushes, it was said. One (E. P.) appears to have been solely a case of poor physical condition, largely resulting from poor eating habits and from unwise use of laxatives.

COMMENT

All in all, therefore, it is clear from the above account that in these instances of induced menopause (10 out of 13 listed in Tables I and II), estrogen alone, or combined with phenobarbital, was without important effect on the purely objective vasomotor phenomena in which we were interested. This was so since neuroses or other conditions of various sorts were present as contributing, rather than coincidental, factors. The mechanism by which nervous elements modify the state of the smallest blood vessels of the skin remains to be defined.

The fact that psychogenic factors may bear a causal relation to the flushes of the surgical menopause suggests several pertinent questions. Why is it, one would like to know, that a neurosis in the presence of normally functioning ovaries does not give rise to the vasomotor disturbances of the menopause, but soon after ovarian deprivation, typical vascular symptoms may appear in intense, aggravated form? Or again, at what level in the brain stem is this wave of vasodilatation of the skin blood vessels with attendant sensation of heat and suffocation set into action? And finally, for what functional change in nerves, skin, or tissues in general does the menopausal flush "compensate" at such an expense of comfort to the patient, and frequently with such inefficiency that the flush is followed by vasoconstriction and an equally uncomfortable sensation of coldness?

TABLE II. PATIENTS EXPERIENCING RELIEF FROM THE MENOPAUSE SYNDROME LARGELY AS A RESULT OF CORRECTING A PSYCHOGENIC, SOCIAL OR MEDICAL PROBLEM

NAME	AGE	MENOPAUSAL OR CLIMACTERIC STATE	PSYCHOGENIC OR OTHER CONTRIBUTING FACTOR TO THE SYNDROME	REMARKS CONCERNING TREATMENT, CONDITION AND RESPONSE	RESULT OF TREATMENT
V. L.	27	Surgical, 11 months' duration	Flushes and sweats occur at irregular intervals; severe. Two such periods occurred when attacked and cut by husband and when injured in a brawl.	Estrogen gave prompt relief, but this was found to coincide with settling poor home situations in court. Some return of flushes when work was resumed and weather was hot.	Relieved except when recurrent exciting circumstances arise. These cause complete return of symptoms, despite level of estrogen dosage. Requires additional treatment. Returned to housework.
D. T.	39	Surgical, 7 months' duration	Flushes, sweats, chills, weakness and trembling occurred on certain days at irregular intervals, almost not at all on others. Found to begin in middle of night. Excessive libido; fears softening of brain as result from masturbation.	Little improvement with estrogen. Complete relief after four days when assured masturbation was not physically harmful, in moderation. Estrogens withdrawn after two weeks; no return of flushes.	Completely relieved of flushes and nervousness. Noted dryness of skin and increased amount of urine; this caused some return of symptoms, but these subsided when situation was explained. Stopped coming to clinic, although seen to be well at later times.
D. M.	38	Surgical, 2 months' duration	Flushes, sweats, result of change in social status after husband lost job. Difficulty with children. Noted ankles and eyes swollen at about two-week intervals; coincided with three to four days before next relief check. Worried over bedwetting habit of seven-year-old daughter.	Very prompt relief when medical aid was given child; diet was supplemented with money for better diet. Recurrence of flushes when husband was put off WPA, and when uterine bleeding recurred.	Relieved, except for occasional intervals when recurrence of home troubles worries her. Then flushes return, despite high estrogen dosage.
J. N.	44	Surgical, 1 year's duration	Flushes and sweats very strong in early afternoon, continue into night; not much troubled in morning. Noted that they commence during lunch hour when she whips son who does not read and will not study (9 years old, third year in first grade). Both anticipate this. Boy was breech, required artificial respiration and "had head operated" soon after birth. Worried also over lack of work.	Very little improvement with estrogen. After nature of case was understood, was advised to refrain from making trouble with son. After two months situation was better. Patient looked well and was nearly relieved of flushes. Secured work again and is still well. Flushes come with hard work and eating meat.	Much improved; treatment withdrawn when patient returned to work.

E. M.	51	Surgical, 2 months' duration	Flushes, sweats, and especially chills to the bone. Hard winters in a cold water flat; grown son will not work. Moderately depressed.	Much relief with estrogen. Never for more than two to three weeks. No success in helping home situation.	Intermittent relief only; marked exacerbation of symptoms at two- to three-week intervals.
C. O.	26	Surgical, 2 months' duration	Difficulty in feeding child; husband unable to work, but unable to obtain relief; apparently kept in state of high tension by interference of mother.	After three months' high estrogen therapy, good results were intermittently obtained as difficulties were intermittently less. Best relief in summer, when mother goes to beach.	Intermittent relief, despite estrogen, until summer when afforded fairly continuous relief from flushes. Symptoms ceased as son attended kindergarten. Estrogen withdrawn after eight months.
R. W.	46	Irradiation, 2 years' duration	Flushes, sweats, and severe arthralgia; involutional melancholia; fear of cancer (associates irradiation of ovaries for menorrhagia with malignancy). Talked much of death and futility of living.	Marked improvement in ten days; estrogen probably helpful, but assurance regarding cancer and physical therapy for arthralgia made a new personality. Libido returned.	Relief from menopausal symptoms, but continued treatment for three months after cessation of flushes. Estrogen withdrawn after nine months.
M. diL.	45	Irradiation, 5 years' duration	Flushes, sweats, chills, anorexia, melancholia; weakness; arthralgia; undernourished and constipated.	Estrogen, with phenobarbital, brought little relief. Advised regarding more adequate diet and withdrawing cathartics. Advised to do more for grandchild.	Moderate and intermittent relief only with continued estrogen.
M. D.	45	Surgical, 3 years' duration	Complete menopause syndrome including melancholia and anorexia. Particularly oppressed and agitated by relief investigator, who thinks patient should work. Outwardly placid, but feels "suffocated" and afraid of people.	Relief from flushes in three weeks. Recurred with induced menstruation and especially with visit of investigator. Relief finally attained when patient went to live with people for whom she formerly worked.	Relieved of flushes temporarily. Requires intermittent treatment.
F. B.	39	Intense menometrorrhagia	Marked premenstrual tension with flushes. Strong libido, desires to hold man, fears pregnancy. Desired artificial menopause. Unable to work due to menorrhagia.	No relief with estrogens or androgens. With assurance of dilatation and curettage and possible ovarian irradiation, prompt relief.	Relieved of flushes. Previous diagnosis on observation in hospital, dementia precox.
E. P.	37	Surgical, 1 year's duration	No specific thing found. Anorexia; piles and hemorrhoids; uses strong cathartics excessively and enemas one to three times weekly.	Advised on diet, and against cathartics. Received but 2 injections of estrogen in one week. Seen in clinic later, reported flushes gone.	Claimed relief from flushes.

To answer these questions, much further work will be required. This will take into account a number of facts, some of which are generally recognized by clinicians while others have only recently been acquired in laboratory studies. For example, the flush is usually observed to accompany several basic conditions: excitement, emotion, exercise, and, sometimes, eating. These, it may be observed, are conditions which measurably increase heat-production by the body, or which affect the mechanisms of heat-loss by the body. Moreover, flushes tend to be more frequent and more intense in some women during warm weather, or at times when they are resting, but fully covered by bed clothes. Such considerations as these suggest either that the menopausal woman is essentially deficient in mechanisms for losing heat easily, or that the centers for regulation of heat-loss by the body may be unduly sensitive to otherwise inadequate stimuli. It, therefore, follows that estrogen, sedatives or correction of neuroses, alone or combined with other therapeutic measures, may be effective in alleviation of the vasomotor menopausal disturbances through the action which they have in facilitating adequate and normal circulation of blood in the skin. The extent to which this is achieved by peripheral circulatory adjustments may be shown by suitable studies, whereas the central effects which therapeutic measures possess would appear to be at the level of the brain stem at which temperature-regulating centers are located. This would point, therefore, to the hypothalamus as the seat,[1, 2] or focus, upon which psychogenic or other bodily influences play, directly or indirectly, with such mischief after surgical removal of the ovaries in women.

SUMMARY

Intensive study was made of a group of eighteen women whose primary complaint was strong, frequent menopausal flushes. Thirteen patients were in artificial menopause, 4 were in natural menopause, and 1 was still menstruating. The patients were divided into two groups, according to the way in which they responded to treatment. Seven (3 in surgical menopause, 4 in natural menopause) responded immediately and well to estrogen therapy, so far as subsidence of the flushes was concerned. Of the remaining 11, 10 were in artificial menopause, 1 was still menstruating. These patients did not respond well to estrogen (or phenobarbital) therapy, but either responded well to correction of a neurosis or other medical problem, or they exhibited signs of such complicating factors with which it was not feasible or possible to deal. In view of currently held beliefs that the most common aspect of the surgical menopause is vasomotor instability without important psychogenic factors, the results recorded in this study are held to be significant. Elucidation of a psychogenic factor as a contributing, and not merely coincidental, factor to the flush of the surgical menopause was possible only in view of the extensive, special study which these patients received.

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A COMPARISON OF THE CLASSICAL AND LOWER SEGMENT CESAREAN SECTION*

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ON SEVERAL occasions in this Society, and from time to time in the medical journals, the statement has been made that the low-flap variety of section gives better results than does the classical.

The claim to better results rests chiefly on three points, a lower puerperal morbidity, a lower maternal mortality and a lower incidence of uterine rupture in subsequent pregnancies.

It is probable that, throughout this country, the total number of classical sections performed is greater than the total number of low-flap sections. Therefore, it is unquestionably true that following all classical sections, there have been more women showing puerperal morbidity, more maternal deaths, and more uterine ruptures in subsequent pregnancies than have been found following all low-flap sections. But have the percentages been higher?

If we assume for the sake of argument, that classical sections outnumber low-flap sections in the ratio of two to one, then the number of women showing puerperal morbidity, the number dying, and the number sustaining uterine rupture in subsequent pregnancies, should be twice as great following classical sections as following low-flap sections, in order that the percentages should be the same. And in order that the percentages should be higher, the total number of these untoward happenings should be not just twice as high but over twice as high.

To me it has seemed possible that the total numbers of these unfortunate consequences of section have been confused with their percentages by those comparing the results of the two types of operation.

Moreover, the classical section antedates the low-flap section by many years, and numerous classical sections have been performed at a period of time when surgery was in a comparatively low state of development. Hence, the results of these early classical sections were less satisfactory.

To arrive, therefore, at a just basis of comparison between the results obtained by classical and low-flap sections, a relatively recent period of time should be selected; and the percentages of results should be estimated from the total number of operations performed by each method.

With this purpose in view, a study has been made of all the sections performed in the Doctors Hospital during the first ten years of its operation. These statistics were compiled from the records by the obstetric resident, Dr. Dean Pinney, from March, 1930, when the hospital opened, to March, 1940.

*Read at a meeting of the New York Obstetrical Society, February 11, 1941.

STATISTICS

In ten years 330 sections were performed in a total number of 5,628 obstetric deliveries, an incidence of 5.8 per cent, or of 1 section in every 17 deliveries.

Of these 330 sections, about 70 per cent were primary, 26 per cent secondary, 3 per cent third sections, and 4, or 1 per cent, fourth sections.

Among the 330, 244, or about 74 per cent, were elective, that is, performed before labor; and 86, or 26 per cent, were performed after labor had started, instead of about three-fourths elective and one-fourth otherwise.

Again, of the 330, 218, or 66 per cent, were classical sections; 100, or 30 per cent, were low-flap sections; 5 were Latzko; 1 was vaginal; and in 6 the type was not disclosed from the records.

The indications for these 330 sections, as given by the operators, not being germane to the discussion, will be dismissed with the statement that about 30 per cent were performed because of previous sections, and 27 per cent because of abnormal pelves, about 8 per cent for previas, and 7 per cent for prolonged labors with little progress; these 4 indications constituted about 72 per cent or nearly three-fourths of all the indications.

The morbidity (temperatures of 100.6° F. for forty-eight hours exclusive of the first twenty-four hours), following these 330 sections, was 63, or 19 per cent. The morbidity of puerperal origin was 55, or 16.6 per cent, and that of nonpuerperal origin was 8, or 2.4 per cent. In this discussion, the puerperal morbidity only will be considered.

The puerperal morbidity following the 244 elective sections was 13.5 per cent; while following the 86 sections performed after labor had started, it was 25.5 per cent, considerably higher as might be expected.

The puerperal morbidity following the 218 classical sections was 12.38 per cent. After the 100 low-flap sections it was 24 per cent, almost twice as high. After the 5 Latzko sections it was 40 per cent. After the 1 vaginal section, there was no puerperal morbidity; and after the 6 with type not stated, 2 women showed puerperal morbidity.

Thus, it is seen that following all of the classical and all of the low-flap sections, the puerperal morbidity was about twice as high in the latter, the low-flap section. This, however, is not conclusive, as it is necessary to know how many elective sections and how many performed in labor were in each type of operation.

In the whole 244 elective sections, 173 were classical and 66 were of the low-flap variety. In 5 the type was not stated. The puerperal morbidity following the 173 sections of the classical type was 10.4 per cent; that following the 66 elective sections of the low-flap type was 19.7 per cent, this percentage again being almost twice as high in the low-flap type. (In the 5 elective sections, the type of which was not known, 2 women showed puerperal morbidity.)

Of all the 86 sections performed after labor had begun, 44 were classical, 35 low-flap, 5 Latzko, 1 vaginal, and in 1 the type was not known. The puerperal morbidity following the 44 sections performed in labor of the classical type was 22.7 per cent; that following the 35 performed in labor of the low-flap type was 31.4 per cent, considerably higher. (Following the 5 Latzko operations, it was 2, or 40 per cent. No morbidity followed the vaginal section or the 1 with type not known.)

Thus, the résumé of puerperal morbidity following classical and low-flap sections shows:

In all classical and all low-flap sections, the puerperal morbidity was 12.38 per cent for the former and 24 per cent for the latter, about twice as high in the low-flap section.

In elective sections of the classical type, the puerperal morbidity was 10.4 per cent. In elective sections of the low-flap type, it was 19.7 per cent, again almost twice as high in the low-flap section.

In sections performed in labor of the classical type, the puerperal morbidity was 22.7 per cent. In sections performed in labor of the low-flap type, the puerperal morbidity was 31.4 per cent, almost one-third higher in the low-flap type.

To remove all doubts as to these results, if the 6 sections, the type of which is not known, are all added to the group of classical sections, the relative percentages

will be changed but slightly. Five of these were elective sections, 2 showing puerperal morbidity. The sixth done in labor showed no morbidity. If these 5 elective sections are all classed with the 173 known elective sections of classical type, the puerperal morbidity will be 11.5 per cent instead of 10.4 per cent as given above. This would still be much lower than the puerperal morbidity of 19.7 per cent, following the elective sections of the low-flap type.

The conclusion, therefore, is that low-flap sections were followed by a higher puerperal morbidity than were the classical in those performed before labor, in electives, in those performed after labor had begun, and in all considered together, in a survey of all the sections performed in ten years by many different operators at the Doctors Hospital.

Maternal deaths following the 330 sections, happily for the Doctors Hospital and unfortunately for comparative statistics, were so few that no real conclusions can be formed concerning the relative merits of the classical and low-flap sections on this basis. But so far as it goes, the advantage is with the classical. In the whole 330 sections, the maternal mortality was 4, or 1.2 per cent, 12 per 1,000.

There was only 1 death in the 244 elective sections, a mortality of 0.41 per cent, or of 4.1 per 1,000. In the 86 sections performed after labor had started, there were 3 deaths, a mortality of 3.45 per cent, or of 34.5 per 1,000, more than 8 times higher. All of these 4 deaths occurred in the known classical or low-flap sections. None occurred in the 5 Latzko, the 1 vaginal, or in the 6 of unknown type.

In the whole 218 classical sections, there were 2 deaths, a mortality of a little less than 1 per cent, 0.97 per cent, or of 9.7 per 1,000. In all of the 100 low-flap sections, there were also 2 deaths, a mortality of 2 per cent, or of 20 per 1,000, over twice that in the classical.

In the 173 elective sections of the classical type, there was 1 death, a mortality of 0.58 per cent, or of 5.8 per 1,000. In the 86 elective sections of the low-flap type there was no death.

In the 44 sections performed in labor of the classical type, there was 1 death, a mortality of 2.27 per cent or of 22.7 per 1,000. In the 35 sections performed in labor by the low-flap method, 2 deaths occurred, giving a mortality of 5.71 per cent, or of 57.1 per 1,000, a mortality two and one-half times higher in the low-flap type.

SUMMARY AND CONCLUSIONS

Thus, the maternal mortality following all low-flap sections was twice as high as that following all classical sections.

In sections performed after labor had begun, the maternal mortality following those done by the low-flap method was two and one-half times higher than those done by the classical method.

In elective sections alone was the mortality less after the low-flap type of section.

However, as has been said, the total number of maternal deaths was so low that conclusions from them cannot be very convincing. And also when the causes of these deaths are studied, a candid opinion must be that the type of section had little to do with the results.

In the whole 330 sections, the only death after an elective operation, performed by the classical method, seemed entirely independent of the type of section employed. The patient was a mental case who jumped out of bed shortly after being returned to her room. Disruption of the abdominal wound resulted. This in turn caused an intestinal obstruction from which she died, operation for relief being too late. This unfortunate result could not have been due to the manner in which the uterus was opened and closed, as the disruption was in the abdominal wound. In my own series of private sections, the only disruption of an abdominal wound occurred following a low-flap operation.

The second death following a classical section, done after labor had started, was the result of hemorrhage and shock. The operation was performed after many hours of labor. There was profuse bleeding. A transfusion of 500 c.c. of blood proved to be insufficient. Before a second transfusion could be given, the patient died. There is no reason to believe that the result would have been different if the low-flap method had been used.

Both deaths following low-flap sections, performed many hours after artificial rupture of the membranes, resulted from sepsis. The results would probably have been the same had classical sections been performed.

It is possibly significant and but fair to state that the only deaths from sepsis occurred after the low-flap type of section.

Rupture of the uterus in subsequent pregnancies following sections did not occur at all during the ten-year period in the Doctors Hospital.

Thus, it is seen that in this ten-year period at the Doctors Hospital, in the 330 sections performed, the results from the low-flap sections have not been better than those from the classical. On the contrary, in this comparatively small group, results from the classical have been better. The puerperal morbidity following the classical has been much less; the maternal mortality much less; and rupture of the uterus in subsequent pregnancies was the same, that is, it was absent in both types.

No attempt is made in this paper to prove that the classical section gives better results than the low-flap section. Proof cannot be made from such a small group of cases. But the evidence is here given that in one hospital, in a ten-year period, with sections performed by many different operators under similar conditions, results following the classical have on the whole been better. True statistics will always add to the sum total of knowledge.

The purpose of this paper, as mentioned, is not to try to settle the question of the superiority of one type over the other, but to submit this evidence in the hope that other observers will be encouraged to give additional information in more and larger groups of sections.

If the low-flap section cannot be shown definitely to give better results than the classical, then it would seem that it should not be given the preference. For the low-flap operation is more difficult to perform. It takes longer. It is usually attended with more bleeding. It carries greater danger of bladder injury. In transverse incisions into the uterus, there is danger of extension into the broad ligaments during delivery. In placenta previa the incision is often made directly into the placental site, in the thinned-out portion of the uterus where hemorrhage is hard to control; while in the classical, the incision may avoid the placental site entirely.

The low-flap type has one advantage over the classical, in that the baby may be delivered by the vertex instead of by breech. This advantage disappears, however, when section is performed for breech presentation.

In short, in the absence of proof to the contrary, the classical would seem to be the better operation. It is easier, quicker, with bleeding under better control, and it carries less danger of damage to surrounding tissues.

For the highly skilled gynecologist, the low-flap section will give good results (possibly no better than the classical). For the great mass of obstetricians throughout the country, many of whom do safe, conserva-

tive, skillful, and satisfactory work, the classical section, in all probability, should give better results than the low-flap section.

In any large series of obstetric deliveries, especially among the upper classes and in this country with its mixed population, Cesarean section is going to be necessary at times, whether the incidence is 2, 4, or 6 per cent. Men well qualified to do 95 per cent of the deliveries will occasionally be confronted with the necessity of doing the remaining 5 per cent by section. Why should they not employ the easiest type of section, the classical, unless the low-flap type is shown to be better?

If the low-flap section were extraperitoneal, the argument for its general use would be stronger. In neglected cases, or in those where labor for various reasons has continued for unduly long periods of time, the Latzko or similar operations, being extraperitoneal, should give the best results. These operations are necessary, however, probably in less than ½ per cent of all obstetric deliveries.

It would seem logical, unless there is proof to the contrary, that the best results might be obtained by the employment of the classical section for general use, supplemented by the Latzko or allied extraperitoneal operations, for the neglected or occasional case.

In closing, may further attention be called to this series of 330 sections which presumably represents a fair cross section of private practice in the better hospitals.

Elective sections were about 3 times as frequent as those performed after labor had begun.

Puerperal morbidity following elective sections was much lower than that following sections performed in labor, 13.5 per cent in contrast to 25.5 per cent.

Maternal mortality, from all causes, following elective sections was 8 times less than that following sections performed after labor had started.

Following 5 Latzko sections, in infected or potentially infected cases, there was no maternal mortality.

Maternal mortality following sections was 9 times higher than that following pelvic deliveries, 1.2 per cent for the former and 0.13 per cent for the latter; in a total maternal mortality of 0.19 per cent in 5,628 deliveries.

From these statistics, three obvious conclusions may be drawn, and a fourth, the point of discussion in this paper, is added:

1. Sections should never be decided upon in the absence of very strong indications, as the maternal mortality is much higher than in pelvic deliveries.

2. It is much better, where possible, to decide upon and to perform section in advance of labor, as the maternal mortality is much less than in sections performed after labor has started and has progressed for hours.

3. Where labor has been in progress for an undue length of time and section is found necessary, extraperitoneal section is the safest.

4. During a ten-year service at the Doctors Hospital, in an admittedly small number of cases, results from the classical section have been better, on the whole, than those from the low-flap section.

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DISCUSSION

DR. GEORGE W. KOSMAK.—Discussions on the comparative efficacy and value of certain obstetric procedures are no more out of line than those witnessed in other fields of medicine. As cesarean sections became more universal, different techniques found adherents, just as in gastrointestinal, prostatic, biliary, brain, thyroid, and other surgical realms. The antagonisms between the urologist who preferred perineal to suprapubic prostectomy, or the general surgeon who condemned cholecystotomy in contrast to cholecystectomy, are by no means adjusted. A similar relegation to the discard has been attempted by those in the low-flap group of "cesareanists," to coin a word. As a matter of fact some of our outstanding obstetric operators have been most disdainful in their comments leveled at those who favored the classical operation. One need only note the caustic remarks in successive editions of the admirable *Year Book on Obstetrics*. It would appear as if the man who did otherwise than a "low flap" was committing a crime.

A carefully studied paper like that of Dr. Ryder constitutes a relief to those who want to be impartial, who are desirous of being guided in their decisions by the final results on patients rather than by the bright and dazzling light of the propagandist for a particular procedure.

Let us look at the record. Dr. Ryder has favored us with a carefully elaborated set of statistics from a hospital of special character in which a cross section of the New York profession, specialist and otherwise, cares for a group of higher income class bracket patients. This may or may not have a bearing on results. However, an incidence of 5.8 per cent, or 1 in every 17 deliveries, impresses one as rather high when compared with the so-called lower income group in our municipal hospitals. This is not intended as a reflection on more conservative indications, but the fact that previous section was done in almost 30 per cent of the patients, must be taken into account in the final decision. Other indications, aside from abnormal pelves, constituted a minority in the final analysis. It is of interest to note, however, that the classical operation was done in 66 per cent and the low-flap operation in 30 per cent of the cases, with about 12½ per cent morbidity in the former and 24 per cent in the latter. If we differentiate between elective and in labor operations, the results again favor the classical procedure. As there were only 4 maternal deaths, two for each type, this factor can be eliminated. Based on the morbidity results, therefore, one cannot disagree with Dr. Ryder's assertion that the classical operation essentially is superior for the type of patient and the type of operator concerned in this service.

There may be no question of course, as Dr. Ryder has shown, that the classical operation in his series, is superior so far as simplicity and final results are concerned. But it will not settle the choice, for operators will continue to be guided by their personal preference. However, his presentation will, if studied carefully, detract somewhat from the laudatory encomiums which have been lavished by enthusiastic proponents upon the newer procedure. An important point, which cannot be set aside, is that cesarean section is a matter of early deliberation and execution rather than a last resort indication. The elements which must be fully considered are hemorrhage, shock, and sepsis and these, if present, are all included in the general designation of morbidity. I believe that a mere rise of temperature should not be regarded as the only item in determining a satisfactory recovery of the patients, and it would have been of interest if we knew how long they had to be kept in bed, the character of the puerperium, complicating conditions, such as anemia, behavior of bladder, and bowels, and a general restoration to health. These would constitute better criteria than a little fever, and we should look forward to an analysis from this point of view.

Personally, I believe that the upper uterine segment is safer for incision than the lower, that the so-called dangerous uterine spill can be avoided, that hemorrhage may be better controlled, the fetus and placenta more readily extracted and, if tubal sterilization is indicated, that it can more easily be carried out. However, I doubt whether either group of operators can be swayed from their position, and if each claims their approach is preferable, they can readily bring statistics to their support. There is always value, however, in controversy; it does prevent the development of too high a degree of self-assurance.

DR. HENRY T. BURNS.—About twelve years ago when the low-flap procedure was gaining popularity rapidly, I did a few and found it took from ten to fifteen minutes longer than the classical section. I observed many other men doing the low-flap cesarean section, and I felt that the anesthesia longer by fifteen minutes and exposure of the abdomen, counterbalanced the good effects that may be obtained by opening the lower uterine segment. I gave up the low-flap operation about ten years ago and have not done it since.

I do two types of low cesarean section and by that I mean making an incision in the abdominal wall as low, I think, as those using the low-flap operation, just above the bladder. In the majority of my cases I do not see the intestines, and I do not feel that much of the spill goes above the broad ligaments because I operate on my patients in the flat rather than in the Trendelenburg position.

The other type is a true extraperitoneal section, the Latzko type of operation, of which I have done 59. In addition I have done 5 by the Waters' technique making a total of 64 true extraperitoneal type of operation, without a maternal death.

DR. BENJAMIN P. WATSON.—The great object in the low-flap procedure is to prevent spill into the abdominal cavity. I have seen many low-flap operations done in which there was just as much spill as in the classical operation.

In an elective cesarean section on a patient who has not been in labor, it is not always easy to get a sufficient flap of peritoneum raised from the lower uterine segment absolutely to shut off the upper peritoneal cavity from spill. The technical difficulty of pushing the bladder down, raising the upper flap and attaching the flap, as it should be attached, may be great, so that trauma may be inflicted upon the connective tissue. Therefore, in doing cesarean section at the time of election, where the patient has not been in labor, I believe that a low classical section will give just as good results as the low-flap section to the experienced operator and better results to the occasional operator. On the other hand, if the patient has been in labor for some time, if the lower uterine segment has been pulled up and the bladder has been pulled up, the low-flap procedure is very much easier. You can get better flaps and you can shut off the upper peritoneal cavity completely. Under those circumstances, the low-flap operation is the better procedure.

With respect to the danger of subsequent rupture of the uterus, I do not believe that there is less danger after the low-flap section than there is after the classical operation, provided the uterine wall is stitched in the proper way when the classical section is done.

DR. EDWARD G. WATERS.—The vast majority of papers on cesarean section in the past ten years seem to indicate that any type of low-flap operation is better by almost any standard than the old classical operation. If a low-flap operation is better in potentially infected cases then it should be a still better operation in clean cases.

At the Margaret Hague Maternity, about 70 per cent of the cesarean sections are of the low-flap transperitoneal type, because it is our experience that these are safer operations, judged by standards of morbidity, mortality, patient's comfort, and operative hazards. We are well acquainted with all of the hackneyed objections to the low-flap operation and the low transverse cervical incision, and have concluded, in an experience of about 1,500 sections, that they exist mainly in the minds of those who do not perform operations of this type.

We have yet to see an actual intra-partum rupture of the uterus where the low transverse cervical incision had been used, despite the fact that 70 per cent of our cases are of that type. Although only about 10 per cent of our cases are classical sections, we have seen five cases of uterine rupture (in a group of 25 ruptured uteri) follow previous classical section. Rupture of the uterus through a low-placed scar must be very rare by comparison with data on classical scars.

Our statistics for a period of four years (1937, 1938, 1939, and 1940), which is a comparable time to Dr. Ryder's carefully analyzed group, show during that period, that there were 21,862 deliveries, of which 737 were delivered by cesarean section, an incidence of 3.3 per cent; about half the incidence reported here tonight. There were 9 deaths, a mortality rate of 1.2 per cent, which is exactly the same as quoted by Dr. Ryder for his group. Those 9 might be corrected down to a group of 4,

where the fault lay with the type of operation performed. The other 5 patients would have died with or without operation, and irrespective of the type done. There were only 35 classical sections, an incidence of 4.7 per cent, done mainly on patients in whom it was felt that no further pregnancy should be permitted and who should be sterilized. There were 3 deaths in the classical section group, a mortality of 8.5 per cent. It may be that we do classical sections so seldom that we no longer know how to do them.

There were 511 low segment operations, an incidence of 69.3 per cent, and in this group there were 4 deaths, a mortality rate of 0.08 per cent.

There were 181 extraperitoneal operations, an incidence of 24.6 per cent, with one death, or 0.5 per cent. These sections were done in potentially and actually infected patients. In this group there were 7 cesarean hysterectomies, an incidence of 0.9 per cent, with no deaths.

Even with a group of 737 cesarean sections, it is very important to remember that percentages do not mean much, for one or two deaths can markedly alter mortality rates. For example, I think the percentage of deaths which Dr. Ryder quoted in the low transperitoneal operation was about 7 per cent in a group of about 66. To judge the value of an operation from the mortality standpoint, the series of cases must be in the thousands to mean much.

DR. RALPH L. BARRETT.—It is all very well to report that the classical section is satisfactory, as in this series. That is true, but if all the series are considered together for the last fifteen years, three series of over 200 or 300 cases in which the classical operation can be shown to have as good a mortality rate as the low-flap operation cannot be found. In general, the low-flap procedure will show less than half the mortality rate of the classical section. We tried it out at the Woman's Hospital on 1,000 cases which were reported before this Society, where the mortality has been cut down in the low-flap operation to five-tenths of one per cent from all causes.

There are some of us who feel very strongly about the low-flap section. We believe that, if it is better for the woman who has been in labor, it is equally good for the woman who has not been in labor.

DR. CLAUDE E. HEATON.—On Dr. Holden's service at the French Hospital which began in April, 1935, there were during the first four years 3,103 deliveries. In this series 125 cesarean sections were performed, a rate of 4 per cent. The operations were done by 22 operators, but about 6 of these operators did 90 per cent of the cases. There were 73 classical operations, 45 low-flap operations, 6 Latzko operations, and 1 peritoneal exclusion. The morbidity for the classical type was 28 per cent; for the low-flap section 26 per cent, and for the extraperitoneal type 50 per cent on the basis of 100° F. One patient died, after a low-flap operation done under local anesthesia for progressive toxemia, of cerebral hemorrhage twenty hours after operation. This gives a mortality rate of 0.80 per cent.

DR. INGLIS F. FROST.—Following the classical operation, adhesions are more likely to occur than in the low-flap procedure. If, in a secondary cesarean operation, adhesions are present, real difficulty may be encountered, especially is this true if these adhesions are marked in the region of the uterine scar. They may also interfere with normal uterine contraction following delivery.

DR. HERVEY C. WILLIAMSON.—The low-flap section is not a difficult operation but just as simple as the classical operation, the only difference being that a few moments must be taken to dissect the flaps and a few more to close them after the uterus is sutured. I have never observed that the low-flap operation caused more bleeding than the classical operation, rather definitely less, especially when local anesthesia is used.

DR. HARRY ARANOW.—I feel much safer in doing the low-flap operation, and after you have trained a group of men to do that particular type of operation, it is not very difficult. I do not think that time is such an important element, whether it be five minutes more or less.

DR. RYDER (closing).—Of those taking part in this discussion, four expressed preference for the classical type of section and five for the low-flap type. I expected the preference to be more decidedly in favor of the low-flap type.

I have examined over 27 recent articles on cesarean section, and in all but one, the preference was in favor of the low-flap type. However, in all of these articles, statistics were lacking to substantiate the preference.

In the November, 1940, number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there appeared an article by Dr. King of New Orleans. In the discussion following, Dr. Falls of Chicago said that he had performed 200 sections in his service alternately by the classical and low-flap methods and that his results were practically identical. This is the only instance found, in the 27 articles read, where an attempt had been made to compare the two types of section performed under similar conditions.

There is no doubt that throughout the country at the present time, the low-flap type of sections is considered better than the classical. I think that this is taken too much for granted. Proof is needed and this proof is lacking.

Any skillful operator doing the low-flap section as a routine will get good results. The question is, would he not get just as good results from the classical?

The teaching at the present time in most of the medical schools is that the low-flap section is the best. All young doctors graduating feel that they must do this type of section. They are not all going to be specialists. Many will be general practitioners in the country. They or any good abdominal surgeon can do a classical operation easily. But if they try to do a low-flap operation, they may get into serious trouble.

It is a good general principle of surgery that if a simple easy operation will do as well, it is a better operation than a complicated and difficult one. As I have said, I am not trying to prove the superiority of the classical operation. This would be foolish from the small number of cases presented. What I am hoping to do is to stimulate interest in this question so that others will submit statistics of the two types of sections performed under similar conditions.

In this city there is a wealth of material. If the doctors in charge of this material would all work up their statistics and present them, we might have reports on 2,000 sections performed by the two methods. Then by a comparison of results, the question of the superiority in these two types of section might be decided.

In closing, I wish to say that I think the results obtained depend more on the operator than on the type of section employed, and that it is unwise to insist that all operators should use one type only, until that type is definitely shown to give better results.

Patton, J. F.: Ureterovaginal Fistula: A New Method of Reimplantation of the Ureter Into the Bladder, J. Urology 42: 1021, 1939.

Sixteen cases of ureterovaginal fistula are presented, six of these coming under the author's personal observation during the past two years.

The importance of early investigation is stressed with application of appropriate therapeutic measures in an effort to preserve the kidney. A thorough urologic study is essential in every case of leakage of urine through the vagina, even when a vesicovaginal or urethrovaginal fistula is obvious. The type of therapy to be applied to ureterovaginal fistula should be determined only after a careful study and should be directed primarily towards preservation of renal function and reestablishment of the urinary channel to approximate its normal state. Nephrectomy should be reserved for the irreparably damaged kidney or as a measure of last resort.

Dilatation should be the first procedure. In event of failure, uretero-ureteral anastomosis is the method of choice in high ureteral injuries and reimplantation into the bladder in low ureteral injuries. A new method of reimplantation of the ureter into the bladder through the intramural ureter which reproduces the normal condition, should be applicable in a definite percentage of cases.

J. P. GREENHILL.

STERILIZATION BY MEANS OF PERITONEOSCOPIC TUBAL FULGURATION

A Preliminary Report

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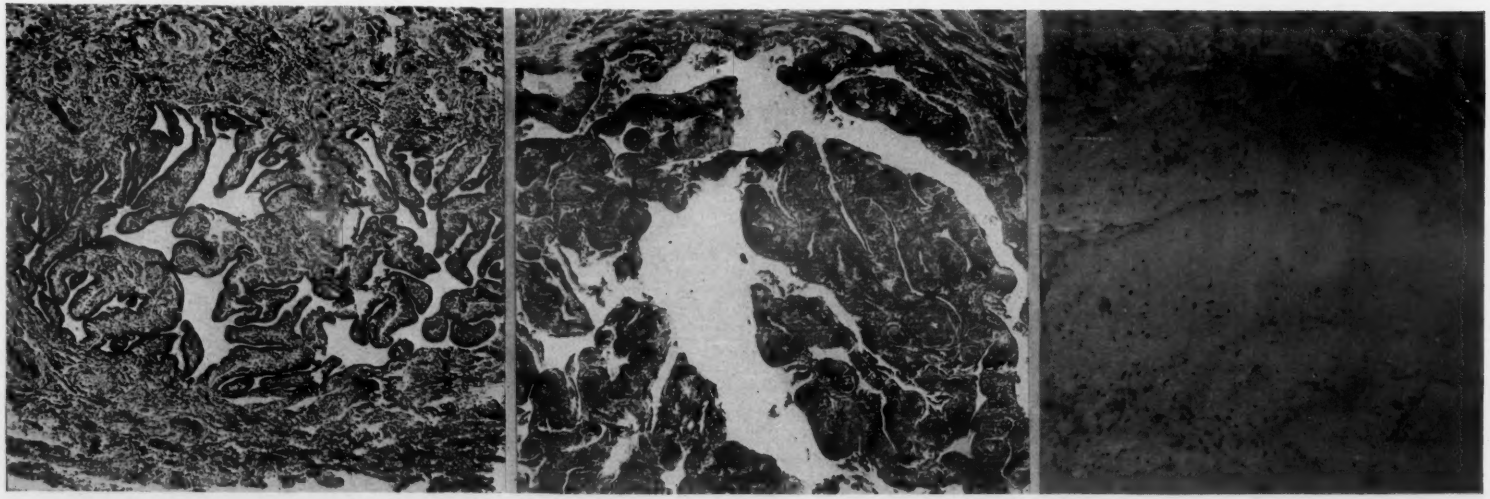
THIS paper concerns itself entirely with a possible technique for sterilization by fulguration of the Fallopian tubes through a peritoneoscope. The many other aspects of the sterilization problem, legal, social, moral, and medical, have already received capable treatment elsewhere in the literature.

Since the first recorded tubal ligation for the purpose of producing sterility by a Dr. Lungren of Toledo, Ohio, in 1880, numerous methods of performing tubal occlusion have been advanced. In general all these methods seek to achieve common objectives, on the basis of which any new technique must also be judged:

1. *Certainty of Prevention of Conception.*—This, obviously, is the ultimate standard by which all methods must be evaluated. Surveys of the literature on this subject, however, reveal some failures with practically every method,[1, 2] the Pomeroy technique apparently enjoying the best position in this respect.[3] No report can be made at this time as to the certainty of the method here to be described, since only the passage of years and the accumulation of a large series of cases can give the ultimate answer.

2. *Preservation of Ovarian Function.*—Sterilization with castration can be achieved simply by radiation or oophorectomy. However, it is often undesirable to precipitate an artificial climacteric, and in this paper, sterilization is taken to mean sterilization without castration.

3. *Simplicity for the Patient.*—Women who are subjected to sterilization fall generally into two groups: A very small group for whom the operation amounts to an elective procedure, and the much larger group for whom pregnancy is contraindicated. For many of this latter group, general anesthesia and laparotomy with a prolonged convalescence are similarly contraindicated. In either group the ideal procedure would be one which could be carried out with a minimum invalidism. From the point of view of the length of required hospitalization, the generally accepted procedures fall into three principal classes: Those requiring laparotomy,[2] those performed vaginally,[4, 5] and bicornuate intrauterine fulguration.[6, 7] Laparotomy, regardless of the exact technique, remains a major intrusion into the peritoneal cavity, with the morbidity, mortality and convalescence commensurate with such procedure.[8, 9] This also applies to the inguinal approach which is tantamount to a bilateral inguinal herniorrhaphy with the added disadvantage that considerable traction must be applied to the tubes at a time when they cannot be directly visualized.[10] Vaginal sterilization by tubal ligation through the anterior or posterior cul-de-sac usually requires two to four days' strict confinement to bed, and five to seven days' hospitalization.[5] Fulguration of the cornual openings of the tubes might conceivably become an office procedure, as claimed by Hyams,[7] presenting a method requiring no hospitalization and minimal invalidism. This method, however, involves a violation of the uterine cavity, which should not



A. *B.* *C.*

Fig. 1.—Sections taken through three consecutive blocks of tissue from treated tube; shown at increasing power of microscopic projection. *A*, Area of normal tube. *B*, Section taken from margin of treated area, showing loss of cell outline and destruction of endosalpinx. *C*, Area of tubal scar showing loss of cell outline, fusion, and hyaline fibrosis.

be regarded too lightly. An interesting contribution to the problem of reducing the convalescence of tubal ligation is the revival by Adair and Brown[11] of puerperal sterilization, combining the postoperative hospitalization of the laparotomy with that of the delivery. This, however, solves the problem for only a select group of patients, and is not in itself without dangers.[12]

4. A fourth criterion which recurrently is suggested as an attribute of the ideal method of sterilization is *reversibility*. Naujoks[13] has summarized the many operations which have been devised for reversible sterilization. Neither the methods most commonly employed nor the one here proposed are designed to be reversible.

TECHNIQUE

The procedure here presented consists of fulguration of the Fallopian tubes through the peritoneoscope, using high frequency, high voltage pulsating current. The technique of peritoneoscopy has been amply described by Ruddock,[14] and in general we have followed his method. The patient is prepared as for laparotomy, and preoperative pentobarbital and morphine given. The patient is catheterized immediately before going to the operating room. Using local anesthesia, a 1 cm.

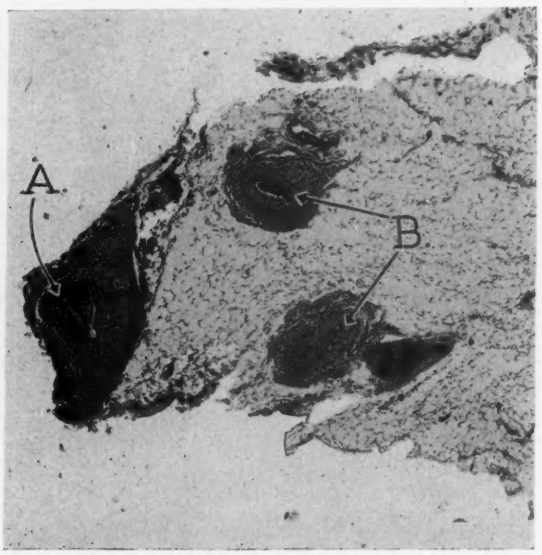


Fig. 2.—Section showing scar of treated area of dog's cornu. *A*, Fibrotic band of tissue. *B*, Local vessels (patent).

incision is made through the skin and anterior rectus sheath just below and to the left of the umbilicus. With the patient in Trendelenburg position a small trochar is inserted into the peritoneal cavity through the tiny wound, a pneumoperitoneum induced with a small rubber hand pump, and the peritoneoscope introduced into the abdominal cavity. Ordinarily one can visualize the pelvic organs satisfactorily, but should any difficulty be encountered, a hand inserted into the vagina can manipulate the uterus to bring the tubes and ovaries into view.[14] Using the biopsy forceps, a Fallopian tube is grasped near the cornu and the fulgurating current applied until a segment of tube 1 cm. in length is blanched. This may be repeated in another location 3 to 5 cm. distally, and the opposite tube is then treated in a similar manner. After general abdominal inspection with the observing telescope unit of the peritoneoscope, the air is released from the abdomen, the peritoneoscope withdrawn and the wound closed with two fine silk sutures. The patient ordinarily remains in the hospital twelve to eighteen hours, and the sutures are removed in about five days.

PATHOLOGY

Six weeks following fulguration, gross examination showed marked fibrosis of the tubes which were contracted to the caliber of a fine cord over a distance of 1 or 2 cm. at each point of treatment. There were a few small adhesions involving one of the fulgurated segments. Cannulization of the normal untreated sections of the tubes revealed the patency of these areas (Fig. 1, *A*). That no fistulas were present was demonstrated by the injection of fluid into the tubes from both the uterine and fimbriated ends.

Microscopic examination revealed destruction of the endosalpinx with marked hyaline fibrosis of the entire tube in that area (Fig. 1, *B* and *C*). Patency of the ovarian vessels was demonstrated to have been preserved. Animal material also removed six weeks following fulguration of the same type but slightly more prolonged, showed reduction of the dog's cornu to thin threads of tissue over the

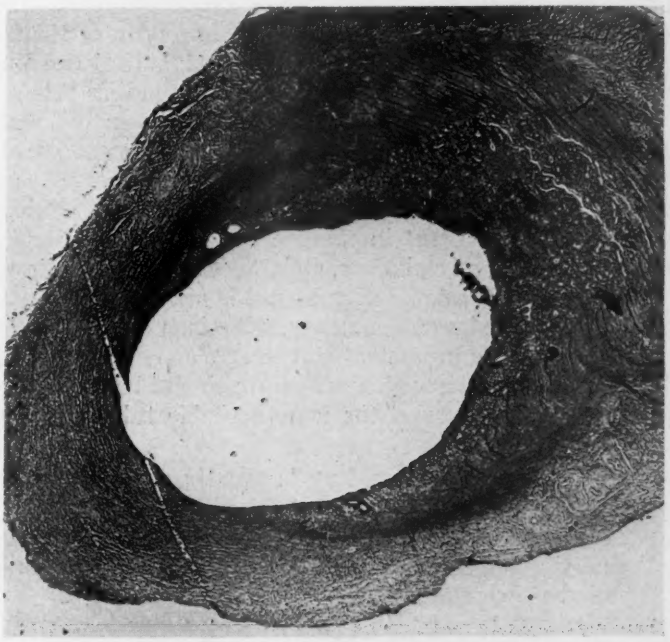


Fig. 3.—Untreated section of dog's cornu.

areas treated. Microscopic examination of sections taken through several of these areas failed to demonstrate any trace of the uterine structure. The fine thread visible upon gross inspection was found to be composed of the uterine vessels and a contracted strand of fibrous scar (Fig. 2). The untreated segments of the cornu demonstrated continued vitality of the endometrium and normal appearance of the cornual wall (Fig. 3).

COMMENT

Cauterization of the Fallopian tubes to produce their occlusion was suggested as early as 1848 by Froriep,[15] who proposed that fused silver nitrate be guided to the uterine horns by hollow conductors. Prudnikoff,[16] in 1912, suggested transuterine coagulation of the cornual stomas as a means of producing sterility. Cauterization or fulguration so employed, however, has the disadvantage that the application is carried out without direct visualization.

Peritoneoscopic fulguration of the Fallopian tubes for the purpose of producing sterilization, has not, to our knowledge, ever before been tried. We do not believe that the literature contains any suggestion concerning this use of the peritoneoscope. We believe that this method warrants further study and clinical trial, because it appears to present certain advantages over various other generally accepted procedures:

Safety.—Ruddock[14] reports accidental perforation of an abdominal viscus in 8 (0.88 per cent) of his 900 cases recently surveyed. All but one of these accidents were attributable to abdominal pathology suspected prior to peritoneoscopy, and which would contraindicate any attempt at peritoneoscopic sterilization. In each case laparotomy allowed prompt repair of the damage and the morbidity was no greater than for simple laparotomy. He reports one death from delayed hemorrhage from liver biopsy, which would not occur with simple fulguration of the Fallopian tubes. In the 175 peritoneoscopic examinations done at the University Hospital in the past three years, a huge liver extending below the umbilicus was perforated, and the colon, adherent to an old scar in the anterior abdominal wall, was entered. Immediate repair was accomplished and recovery was uneventful in both instances. Since the procedure is performed under local anesthesia and with very minimal tissue damage, the dangers inherent in the use of general anesthesia and the likelihood of postoperative embolism, atelectasis and pneumonia are eliminated. The danger of postoperative hernia is nil. In those cases where laparotomy has followed peritoneoscopy, adhesions to previously cauterized areas has not been a prominent feature. We see no reason to believe that adhesions resulting from this procedure should be any more serious than those which form around the nonabsorbable tubal ligature of the Madlener operation.

Economy.—Although the procedure is usually performed in an operating room equipped with instruments readily available for prompt laparotomy in event of accident, the expense is considerably reduced through the elimination of charges for general anesthesia, assistants, and prolonged period of hospitalization.

Effectiveness.—While, as discussed above, the ultimate test of effectiveness of a sterilization method must rest with the accumulation of a large series of cases, observed for several years, the effectiveness of this method to produce tubal occlusion cannot be doubted. Only after further study and clinical application can we evaluate the place of this procedure in the field of sterilization.

CONCLUSIONS

1. A possible method of sterilization is presented, based on the production of Fallopian tubal occlusion by multiple local fulgurations through a peritoneoscope.

2. Pathologic material from both human and animal subjects is presented to demonstrate the effectiveness of the method in the production of tubal occlusion.

3. By such a method of sterilization, morbidity, length of convalescence, and total expense can be reduced to a minimum.

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STUDIES IN PELVIC IONTOPHORESIS OF A CHOLINE COMPOUND*

II. PREOPERATIVE MANAGEMENT OF UTERINE MYOMAS COMPLICATED BY PELVIC INFECTION, WITH A REPORT OF 39 CASES

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MYOMAS of the uterus are frequently associated with inflammatory disease of the tubes and ovaries.

Kelly and Cullen,[1] in 934 cases, found one or both tubes adherent to the tumor in 423. The frequency in negresses was nearly twice that in white women. The incidence of association in colored women is reported by Miller[2] in 150 cases as 93 per cent, by Alsobrook[3] in 1,000 cases as 99.1 per cent, and by Witherspoon and Butler[4] in 125 cases as 100 per cent.

Keene and Kimbrough,[5] however, found inflammatory lesions in 23.3 per cent of their cases, and Baer and his associates[6] found tubal pathology in only 13.3 per cent of 938 cases. These authors do not indicate the ratio of colored to white women in their cases. Schmitz,[7] reporting the mortality of 3,129 supravaginal hysterectomies performed for myomas at the Cook County Hospital, where about half of the patients are negroes, found that pelvic inflammatory disease complicated 38 per cent of their cases, and showed that it contributed heavily to the mortality. In this large series, there were 78 deaths, a mortality of but 2.1 per cent, yet in 85 per cent of the deaths, or 68 cases, the myomas were associated with pelvic inflammatory disease. Greenhill,[8] in the same type of cases, found that the mortality was ten times as great as for simple supravaginal hysterectomy. There is good evidence for marked increase in morbidity as well.[7, 9]

Removal of the inflamed adnexa, distorted and often adherent to the pelvic walls and intestines as well as the uterus, with collections of pus within or about them, adds greatly to the risk of operation by increasing the difficulty of pelvic surgery and by provoking dangerous peritonitis. Infrequently these lesions are caused by spread of infection from the tumor itself, but generally infection comes from without, either specific in origin or following abortion or parturition.

*Read at a meeting of the Brooklyn Gynecological Society, February 7, 1941.

Women with myomas admitted to the hospital with a history of pelvic pain, elevated temperature, leucocytosis, and accelerated sedimentation time are not good risks for operation. Adnexal pathology may be suspected, yet diagnosis may not be easy when myomas fill the pelvic cavity, and occasionally conditions within the tumor itself, such as degeneration, may account for the same clinical picture.

It has been our experience that strict insistence upon a sedimentation time of eighty minutes is an excellent criterion of relative safety. Slight leucocytosis may be disregarded, but operation should be deferred until the temperature and sedimentation time are satisfactory. It is our experience that normal sedimentation is re-established very slowly, however, when disturbed by degenerative processes within the tumor, and contraindication to operation is not present as in adnexal disease. The period of preoperative observation may be shortened if the nature of the complication is known.

In the course of our studies in iontophoresis of a choline compound, we have reported our results in the treatment of pelvic infections[10] and have fully described the rationale and technique of the therapy. Systemic reactions have also been reported. Our results in tuboovarian infections have been sufficiently good to warrant continued use of this method of treatment when operation and other methods of therapy are not indicated.

CASE MATERIAL

During the past two and one-half years, 39 women with myomas and clinical evidence of pelvic inflammatory disease, or tumor degeneration or both, were given iontophoresis therapy; 37 cases are from the Kings County Hospital, and 2 cases from the Long Island College Hospital.*

All but 5 were negresses; 22 were multiparas, and 17 primiparas, 7 of whom gave a history of abortion. The ages ranged from 35 to 50 years in 21 cases, from 25 to 34 years in 13 cases, and from 18 to 24 years in 5 cases.

In 32 cases abdominal tenderness or peritoneal rebound pain was noted, and in 27 cases a firm mass could be felt in the abdomen. In 18 cases the mass was larger than a five months' pregnancy, and in 9 cases the size of the mass approximated a pregnancy of three to five months' duration. Pain was a prominent symptom in 32 cases. In 12 cases there was a clear history of previous specific infection, and 4 women had suffered complications following induced abortion. Tender adnexal masses were present in 25 cases.

The temperature was above normal in 25 cases, generally between 100° and 102° F. Anemia was uncommon; in only 8 cases was the hemoglobin below 70 per cent Sahli, and in each of these it was at least 60 per cent. In spite of evidence of pelvic infection in 32 cases, leucocyte counts were generally low, above 10,000 and not higher than 15,000 in only 13 cases, though the count was 23,300 in one case. The polymorphonuclear differential count followed the total leucocyte count in its variation.

Sedimentation time was a much better index of the presence and activity of infection. In all but two cases it was accelerated. The normal figure according to the method we use is eighty minutes plus for a drop of 18 mm. of the erythrocyte mass in the sedimentation time tube. The time noted on admission to the hospital is shown in Table I.

In 28 cases the diagnosis of adnexal disease associated with uterine myomas was made, yet in 4 of these cases unsuspected degeneration of a fibroid was present as well, in 1 case proving to be the sole complication. In 8 cases the differential diagnosis could not be made. At operation, degeneration alone was found in 1 case, pelvic infection alone in 4 cases, and both degeneration and infection in 3 cases.

*We are indebted to Dr. William A. Jewett and Dr. Harvey B. Matthews for permission to use these cases.

TABLE I. SEDIMENTATION TIME ON ADMISSION

TIME	NO. OF CASES
7 to 20 minutes	12
20 to 40 minutes	14
40 to 60 minutes	11
60 to 80 minutes	2
Total	39

In only 2 cases was the clinical evidence definite enough to warrant a diagnosis of degeneration alone, and this was confirmed at operation. In 1 case, in which the sedimentation rate was forty minutes, no cause was found at operation.

Hysterectomy was performed in 32 cases, with removal of one or both adnexa in 27 cases. The high percentage of operation afforded an excellent opportunity for ascertaining the type of pathology treated. In every case the possible effect of iontophoresis was carefully studied, and all excised tissue subjected to gross and microscopic examination.

In 11 cases myomas in varying stages of red degeneration and liquefaction necrosis were found, and in 4 of these cases no evidence of pelvic inflammation could be demonstrated. Edema and congestion were occasionally observed. In the adnexal inflammation group, there were 5 cases of pyosalpinx or ovarian abscess.

In 12 cases marked edema and congestion were observed on histologic examination of the tubes, and hyperemia of the pelvic peritoneum and occasionally petechial hemorrhages of the serosa of the uterus were noted at operation. Recent experiments in which iontophoresis had been given a few hours prior to laparatomy for pelvic pathology not associated with infection indicate that these findings can be duplicated.

At first it was thought best to allow a reasonable time for the usual bed rest improvement, before instituting iontophoresis. So, in 7 cases, at least two weeks elapsed before special treatment. Later, when we thought iontophoresis valuable in shortening preoperative preparation, it was given earlier, though in 9 cases, five days at least elapsed. An average of six treatments was given, one every other day. Twelve was the largest number of treatments given to one patient.

Operation was performed when the clinical objectives of normal temperature over a period of time, normal leucocyte count with normal polymorphonuclear differential and normal sedimentation time were achieved. If temperature remained normal over a period of one or two weeks, yet sedimentation time failed to reach normal, laparotomy was performed in spite of this finding, for we assumed that degenerated myomas rather than pelvic infection would be found. Brief history of the following two cases will illustrate:

CASE 1.—M. D., colored, aged 34 years, was admitted to Kings County Hospital on Jan. 29, 1939, with a history of vaginal spotting and right lower quadrant pain for one week. Temperature was 101° F., leucocyte count 12,400, hemoglobin 73 per cent Sahli, and sedimentation time twenty minutes. A hard smooth tender mass rising to the umbilicus was felt in the abdomen. The impression was degeneration of a myoma.

Temperature became normal two days later and remained so. Iontophoresis was begun on February 10, and four treatments were given during the next ten days. Sedimentation time remained twenty minutes. Supravaginal hysterectomy was performed on February 27. At operation, no pelvic inflammatory disease was seen; two huge fibroids were found, the larger showing extensive red degeneration. Postoperative recovery was smooth.

CASE 2.—E. L., colored, aged 39 years, was admitted to Kings County Hospital on July 27, 1939, with a history of progressive enlargement of the abdomen for ten months and discomfort in the abdomen for three months. Examination showed a large, tender, multinodular mass fixed in the lower abdomen. The leucocyte count was 7,600 with 54 per cent polymorphonuclears, 74 per cent Sahli hemoglobin, and sedimentation time sixty minutes. She remained afebrile for three weeks, but the sedimentation time became forty minutes. Iontophoresis was begun on August 23, and 7 treatments were given during the next nineteen days.

Supravaginal hysterectomy with removal of both tubes and ovaries was performed on September 20. The uterus was as large as a six months' pregnancy and studded with fibroids, with thickened tubes adherent posteriorly. Many tumors were in varying stages of red degeneration and liquefaction necrosis. Histologic examination of the tubes and ovaries showed adhesions, edema, and fusion of contiguous folds in the tubal lumina. No inflammatory cells or exudate were seen, and it is possible that hyperemia and edema were due to treatment. Postoperative course was febrile, the temperature reaching 101° F. She was discharged well on the thirteenth day after operation.

In our experience, myomas with degeneration have responded unfavorably to iontophoresis, and we have made use of this finding in arriving at a diagnosis (Table II).

TABLE II. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. DEGENERATION OF MYOMAS

TYPE OF DEGENERATION	NO. OF TREATMENTS	TIME PERIOD (DAYS)	CHANGE IN SEDIMENTATION TIME (MINUTES)
Red, extensive	4	10	20 unchanged
Red and liquefaction	7	28	40 to 22
Liquefaction	9	28	45 to 20
Liquefaction	4	42	20 to 15

TABLE III. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. MYOMAS ASSOCIATED WITH PELVIC INFLAMMATION

ADNEXAL PATHOLOGY (LABORATORY)	NO. OF TREATMENTS	DAYS	CHANGE IN SEDIMENTATION TIME (MINUTES)
Pyosalpinx; chronic salpingitis	4	8	20 to 80
Edema of tubes	8	20	27 to 80
Acute and chronic salpingitis	9	25	21 to 80
Healed salpingitis and perisalpingitis	4	10	20 to 80
Subacute and chronic salpingitis; abscess	6	17	35 to 80
Subacute and chronic salpingitis; pyosalinx	5	10	35 to 80
Subacute salpingitis	5	14	40 to 80
Peri-oophoritis	7	14	20 to 75
Subacute and choronic salpingitis	6	16	40 to 76
Subsiding adnexal infection	3	5	60 to 80
Subacute and chronic salpingitis; large cyst	8	25	12 to 22

Women with pelvic inflammation and myomas not undergoing degenerative changes responded very well to iontophoresis as a rule. Pain was relieved in 75 per cent of the cases. Sedimentation time response is noted in 12 cases in Table III. All these patients were operated upon, and all uteri, tubes, and ovaries were examined microscopically.

An example of the type of response seen in this group follows:

E. S., colored, aged 45 years, was a patient in Kings County Hospital for two weeks in June and July, 1937, with a diagnosis of myoma of the uterus complicated by pelvic inflammatory disease. After a febrile course with temperature reaching 103° F., she signed her release.

She was readmitted on April 11, 1939, with a temperature of 100.4° F., complaining of lower abdominal pain. Examination showed tenderness in both lower

quadrants of the abdomen, the uterus enlarged to the size of a two and one-half months' pregnancy, and a tender adnexal mass posterior to the uterus. The leucocyte count was 6,000 with 71 per cent polymorphonuclears, hemoglobin 74 per cent, and the sedimentation time twenty minutes.

Pelvic iontophoresis was given four times between April 14 and April 20. The sedimentation time on April 19 was more than eighty minutes.

Supravaginal hysterectomy, with bilateral salpingo-oophorectomy, was performed on April 24. The uterus was enlarged by myomas to the size of a two and one-half months' pregnancy, and both tubes and ovaries were densely adherent in the cul-de-sac. One tube was the site of a pyosalpinx, the other tube showing evidence of chronic salpingitis. On histologic examination, edema and marked dilatation of blood vessels were seen. Postoperative recovery was smooth. (Fig. 1.)

When degenerating myomas were associated with pelvic inflammatory disease, a variety of results were obtained as shown in Table IV.

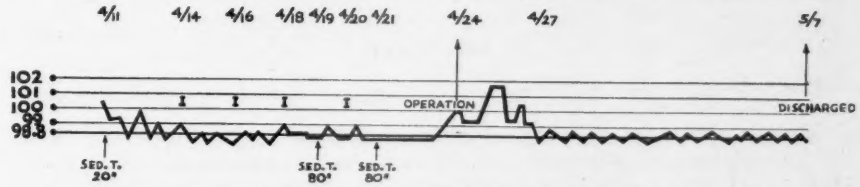

Fig. 1.—E. S. Fibroid uterus with pyosalpinx. Supravaginal hysterectomy and bilateral salpingo-oophorectomy. Smooth postoperative course. *Sed. T.*, sedimentation time; *I*, iontophoresis.

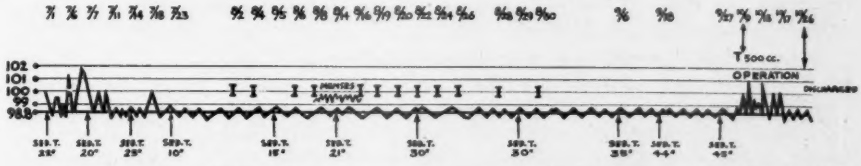

Fig. 2.—M. W. Multinodular fibroid uterus with degeneration and massive pelvic and abdominal infection. (Bilateral pyosalpinx, ovarian abscess, and generalized peritoneal adhesions.) *Sed. T.*, sedimentation time; *I*, iontophoresis; *T*, transfusion.

One of these cases is briefly reported since, after a control period in the hospital of one month, with sedimentation time becoming more rapid; improvement coincided with iontophoresis therapy. Her progress is shown in Fig. 2.

M. W., colored, aged 29 years, was admitted to Kings County Hospital on July 1, 1939, complaining of abdominal pain and vaginal bleeding for fifteen days. Examination showed a huge multinodular mass filling the pelvis and rising 7 cm. above the umbilicus. X-ray showed elevation and flattening of the dome of the diaphragm. Temperature was 99.6° F., leucocyte count 23,300 with 78 per cent polymorphonuclears, hemoglobin 71 per cent Sahli, and sedimentation time twenty-two minutes.

After bed rest for one month, sedimentation time was ten minutes, temperature rising occasionally to 101.8° F. Iontophoresis was given eight times between August 2 and August 30. Sedimentation time rose to forty-four minutes on September 18, and forty-five minutes one week later.

On October 9 supravaginal hysterectomy with removal of both adnexa was performed. The tumor was adherent to sigmoid, transverse colon, and stomach; two large pyosalpinges were present. Peritoneal adhesions were fibrinous, separating easily, with small pockets of clear serous fluid between them. Postoperative recovery was smooth. (Fig. 2.)

The pathologic report showed myomas in various stages of degeneration, including edema, red degeneration, and calcification; the adnexa showed bilateral pyosalpinx and ovarian abscess.

TABLE IV. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. DEGENERATION OF MYOMAS AND PELVIC INFLAMMATION

TYPE (LABORATORY)	INFECTION (LABORATORY)	NO. OF TREATMENTS	DAYS	CHANGE IN SEDIMENTATION TIME (MINUTES)
Red and liquefaction	Perisalpingo-oophoritis; hydrosalpinx	5	11	30 to 80
Red, subsiding	Perisalpingo-oophoritis	1	9	30 to 80
Red, subsiding	Subacute and chronic salpingitis	6	30	23 to 70
Hemorrhage and edema	Subacute and chronic salpingitis	3	4	25 to 75
All types	Bilateral pyosalpinx; abscess	12	30	10 to 35
Hemorrhage and edema	Perisalpingitis; hydrosalpinx	3	11	45 to 15

MORTALITY

Death in one case, clearly not due to iontophoresis therapy, is reported:

W. L., colored, aged 43 years, was admitted to Kings County Hospital on July 8, 1939, complaining of abdominal pain. The uterus was nodular and the size of a three and one-half months' pregnancy; motion caused pain. A tender adnexal mass was palpated. Sedimentation time was twenty minutes.

Iontophoresis therapy was begun on August 12 because of persistence of rapid sedimentation time. Five treatments were given before September 1, with a rise in sedimentation time to fifty minutes.

Supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed on September 26. At operation the uterus was enlarged to the size of a three months' pregnancy by myomas, and both adnexa were involved in bilateral chronic inflammatory masses which were adherent to the posterior surface of the uterus and to the peritoneum of the cul-de-sac. During the course of the operation, a large hematoma formed in the right broad ligament.

The pathologic report described myomas of the uterus and diffuse subacute and chronic salpingitis with perisalpingitis and peri-oophoritis.

On the day following operation when the patient appeared to be in good condition, she suddenly went into collapse, showed muscular twitchings of the face, and died. Death was thought to be due to postoperative embolism.

EVALUATION OF IONTOPHORESIS THERAPY

Our estimation of the value of pelvic iontophoresis is based upon unusually rapid improvement in the clinical and laboratory data significant of infection. Subsidence of fever, pain and abdominal tenderness, diminution in size of inflammatory masses, and more favorable leucocyte counts and sedimentation rates have been the criteria of improvement.

It is clear of course, that subacute or chronic pelvic inflammatory disease, whether associated with myomas of the uterus or not, tends to improve on bed rest alone.

In our opinion it is impossible to set up a parallel series in study of the effect of any method of therapy in pelvic inflammatory disease. Adnexal pathology varies so widely that lesions apparently similar are not identical in histology, bacteriology, or type, character and location of associated pelvic exudates. Observation of approximately 500 cases

of pelvic infection a year in our wards at Kings County Hospital has made us reasonably familiar with what to expect from bed rest, transfusion, and supportive therapy. Not infrequently rapid sedimentation time is the only indication of complication. On the basis of objective findings alone, we have classified our results in all 39 cases.

1. Good effect: When response has been striking.

2. Doubtful effect: When response has been good, but no better than we have seen occur with ordinary supportive therapy.

3. No effect: When the condition remained essentially unchanged.

4. Untoward effect: When clinical evidence of exacerbation of infection or degeneration followed therapy.

TABLE V. EFFECT OF IONTOPHORESIS IN MYOMAS OF THE UTERUS

EFFECT	PELVIC INFLAMMATION	DEGENERATION	COMBINED
Good	11	–	4
Doubtful	7	–	2
Untoward	2	3	1
None	5	1	–

In 3 cases with questionable complication, 2 had a good and one had a doubtful result.

The best results were obtained in cases of myomas associated with pelvic inflammatory disease. No result at all or exacerbation of symptoms followed use of iontophoresis in cases of myomas with degeneration.

We believe that iontophoresis is a valuable method of therapy for chronic pelvic inflammatory disease associated with uterine myomas. The preoperative time is shortened and the risk of operation decreased. Our experience with iontophoresis in degenerated myomas is limited, yet it may be a new aid in diagnosis of difficult cases.

SUMMARY AND CONCLUSIONS

1. We have called attention to the risk of operation when myomas are associated with pelvic inflammation.

2. Pelvic iontophoresis was given during the preoperative preparation of 39 cases of myomas of the uterus, associated with pelvic inflammatory disease, degeneration of myomas, or both. Hysterectomy was performed in 32 cases, and in 27 one or both tubes and ovaries were excised.

3. Material for pathologic study was available, thus affording an excellent opportunity for determining the type of pathology treated and the effects produced.

4. The preoperative preparation of myomas associated with pelvic inflammatory disease may frequently be shortened by this method of therapy, and the operative risk decreased.

5. In cases of myomas complicated by degeneration, iontophoresis either had no effect, or accentuated the degenerative processes.

6. In cases of myomas, where the differential diagnosis between accompanying infection and degeneration is difficult, iontophoresis may be helpful in preventing undue preoperative delay while awaiting satisfactory laboratory data.

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DISCUSSION

DR. MORRIS GLASS.—From Jan. 1, 1935, to Dec. 31, 1940, 610 uteri have been removed by the College Division at the Kings County Hospital; 49 vaginally and the remaining 561 through the abdomen. The abdominal hysterectomies were divided as follows: 473 supravaginal operations; 5 patients died, yielding a mortality of a little more than 1 per cent. The remaining 88 were total hysterectomies, and in this group 4 patients, or 4.5 per cent, died. In analyzing the 9 deaths it was noted that 6, or 66⅔ per cent, were associated with fibroids having pelvic inflammation. In addition, 4 of the patients eviscerated postoperatively, which undoubtedly was a major factor in causing death.

Two procedures have been instituted recently in the hope of decreasing our mortality. The first of these was pelvic iontophoresis. For the past two and one-half years, this form of treatment has been used, as mentioned tonight, on patients with fibroids complicated by inflammatory adnexal masses. It would appear from the results that the preoperative stay in the hospital might be shortened, the masses tend to become smaller, less tender and more mobile and the cellulitic involvement less pronounced. All of these factors would tend to decrease the difficulties at operation and lead to a smoother and less complicated postoperative course. It is plausible to presuppose, however, that pelvic iontophoresis would have no effect whatsoever on large fibroids in which extensive degeneration had taken place, because of the marked disturbance of the blood supply in the tumor.

The second important addition to our armamentarium in reducing the mortality, we feel, is the decrease of wound disruption as a postoperative complication. Since November, 1939, all laparotomies, unless a specific contraindication existed, have been sutured throughout with interrupted fine black silk, including the peritoneum. During this period there has been no evisceration on our service. We feel that the elimination of this formidable complication has helped us improve our end-results attested by our hysterectomy figures for the year 1940, during which time 88 supravaginal and 33 total hysterectomies were performed without mortality.

Guimaraes, P. Duarte. A Case of Intra-peritoneal Hemorrhage of Ovarian Origin, Rev. de gynec. e d'obst. (Rio de Janeiro) **2:** 20, 1940.

The author reports the history of a girl 17 years old with a clinical history of recurrent appendicitis. At operation, the ovary on the right side was found to be ruptured and bleeding; the abdominal cavity was full of blood. The ovary was not removed, but the rent in it was sutured. The patient recovered. The author discusses at great length the differential diagnosis between appendicitis, follicular hemorrhage, ectopic pregnancy, etc.

Mario A. Castallo.

PARAURETHRAL FIXATION

A New Operation for the Cure of Relative Incontinence of Urine in Women

Samuel Gordon Berkow, M.D., Perth Amboy, N. J.

"Paraurethral fixation" is a modified combination of two procedures long used for the relief of urinary incontinence in women. These procedures are: (1) advancement of the urinary meatus to just below the clitoris, as recommended by Pawlik, Dudley and others, and (2) suburethral reefing.

Reports on either type of operation alone claim numerous successes and admit some failures. But my personal experience, limited to suburethral imbrication and the Kelly stitch, has been disappointing. Recent literature indicates that the "few failures" comprise from 15 per cent to 40 per cent.

The first step of the operation proposed elevates the lax urethra, increasing its length and narrowing its lumen; the second step buttresses the lengthened urethra with two layers of muscle, the pubococcygeal fibers of the levators* forming the first layer, and the bulbocavernosus muscles the second layer.

The primary object of this operation is not merely to fuse two techniques. The satisfactory results of parametrial fixation in uterine prolapse prompted the application of similar principles to the surgery of incontinence. More directly, therefore, the new operation is derived from the technique of parametrial fixation, as described by Dr. Robert T. Frank. For this reason, the name paraurethral fixation, suggested by Dr. M. A. Goldberger, has been adopted for this operation.

In the past five years, 21 patients have been operated upon by me with this technique. All of these patients had relative or "stress" incontinence. Two patients were operated upon within the past month, and although they are now continent, a longer time must elapse before the results can be properly evaluated. The first patient and one other were not relieved. In the remaining 17 patients complete bladder control was restored. When these patients were last seen, two months to nearly three years after operation, incontinence had not recurred in a single instance.

TECHNIQUE

After due preparation, with the patient in the lithotomy position, each labium is fastened laterally with a suture. A traction suture is placed just below the clitoris, and another is placed carefully in the vaginal mucosa below the urethral opening of the bladder. This point need not be defined exactly. Sufficient exposure will be obtained if this suture is placed about 5 cm. below the external urinary meatus. The traction sutures are not tied. Upward traction on the superior suture and down-

*Variously named in gynecologic literature (pubocervical muscles, fascia pubocervicalis, pubovesicocervical musculofascial sheath), these structures are anatomically the median fibers of the pubococcygeus muscles, part of the levator sling.

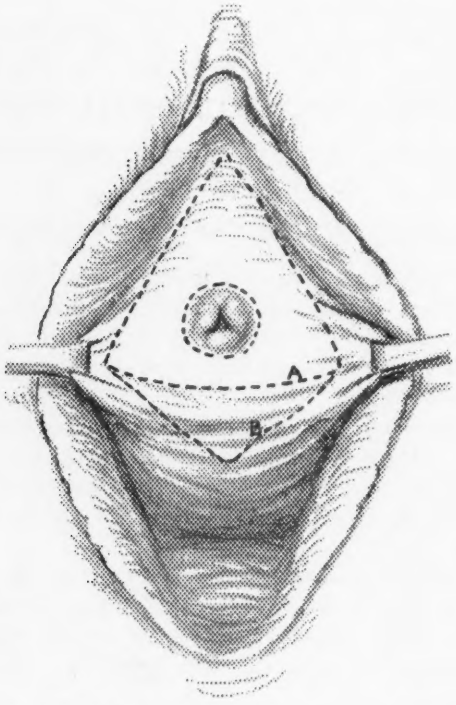

Fig. 1.—Incisions in the vestibular and vaginal mucosa. These sketches depict a secondary operation for incontinence, in which a previous operation cured an associated cystocele without establishing bladder control. *A* shows the lower part of the incision in this case. *B* shows the lower part of the incision as usually made.

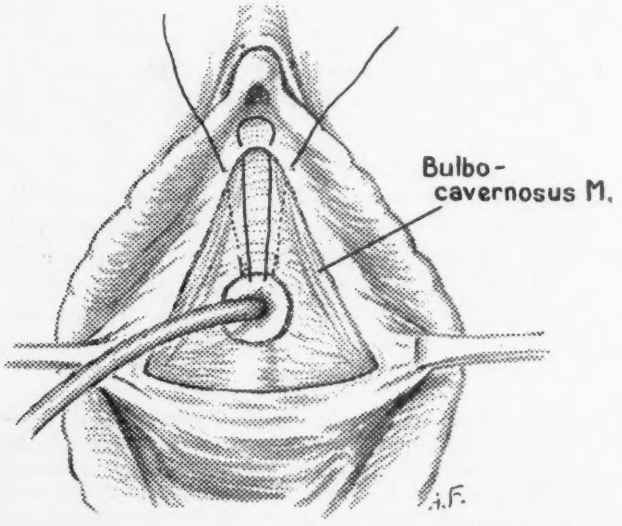

Fig. 2.—Retention catheter in place. Vestibule and adjacent vagina denuded, except for one-eighth inch of mucosa left around the meatus. A Bonney (fixation, or "W") suture replaces the anterior traction suture. Urinary meatus is brought up under the clitoris. This suture is not tied at this time.

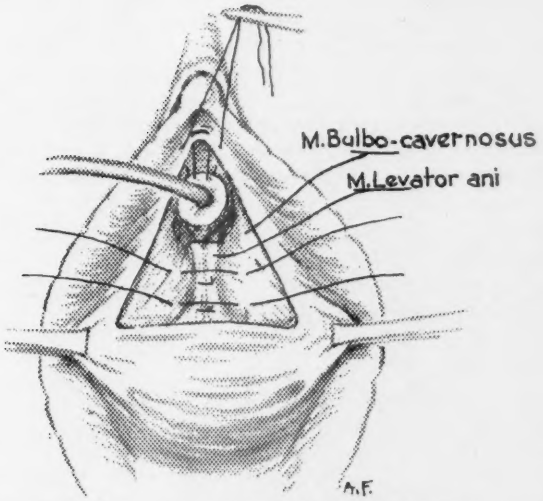

Fig. 3.—Urethra pulled up (for purposes of illustration, the mucosal rim around the meatus has not been pulled up to the mucosa below the clitoris). First row of reefing sutures, bringing the pubococcygeal fibers of the levators together under the urethra. The highest of these sutures should be at, or just behind, the inferior margin of the symphysis. Second row of reefing sutures in place, not tied.

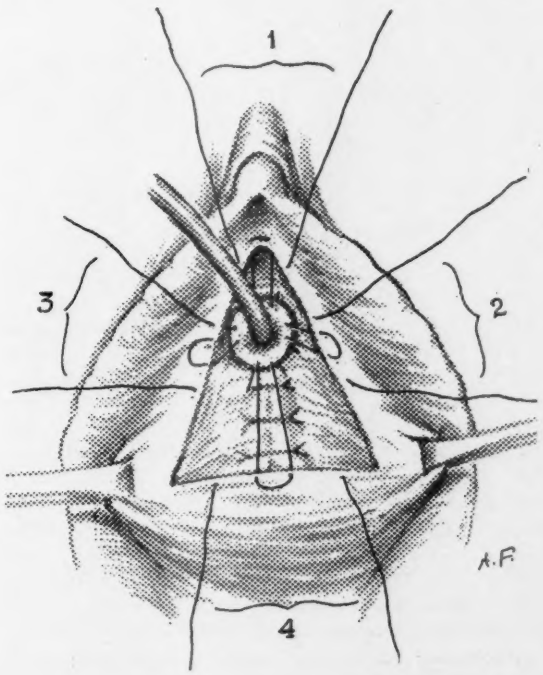

Fig. 4.—Second row of reefing (or buttressing) sutures tied, bringing the bulbocavernosus muscles together under the urethra. These sutures cover the sutured pubococcygeus and extend up on the anterior surface of the symphysis to the meatus. The paraurethral fixation sutures are inserted as numbered, and tied in the following order: 2, 3, 4, 1.

ward and outward traction on the inferior suture brings the quadrilateral area of the vestibule and anterior vagina into a single plane. Keeping the whole area under sufficient tension, the quadrangle is outlined by a mucosal incision. This starts below the clitoris, runs parallel to the retracted labia minora and then downward and medially to the vaginal mucosa just above the lower suture. A second incision encircles the urinary meatus about one-eighth inch from the orifice. By sharp and blunt dissection, the area delimited by these incisions is denuded of its mucosa (Fig. 1). A self-retaining catheter inserted into the bladder aids the suburethral denudation.

Now a Bonney ("W") suture in the upper angle of this incision replaces the superior traction suture. Twisted silk has been used in this suture, but chromicized catgut (No. 2) has proved equally satisfactory. This suture is best started through the apex of the incision, passing through the mucous membrane close to the cut edge.

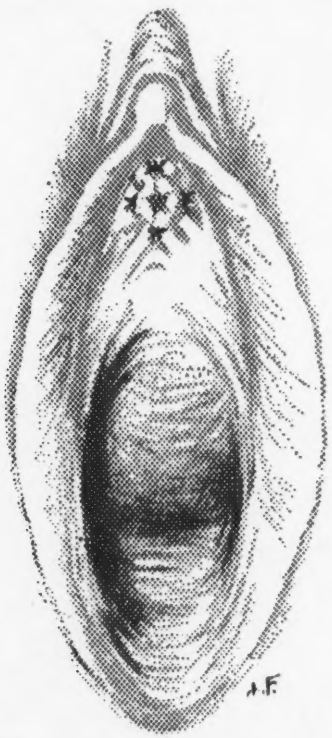

Fig. 5.—Operation completed. Catheter removed. (It is better to leave it in for forty-eight hours.)

Each end of this suture, threaded on a curved cutting needle, is brought down to the urinary meatus, and is carried deeply upward and laterally through the bulbocavernous muscle on its own side, to emerge on the vestibular surface about one-fourth inch from the median line and as far in from the cut surface as possible (about one-half inch). The free ends of this suture are caught in a single clamp.

The mucosa surrounding the meatus is now grasped with a dissection forceps. By traction on the suture and the forceps, the urethra is brought up under the clitoris, until the cut mucosal surfaces are opposed. If the urethra cannot be elevated readily, it is necessary to free the urethra with the back of the scalpel by gentle pressure against the lateral attachments of the urethra. An assistant holds the urethra in the new position by continued traction on the clamp holding the free ends of the W suture.

Starting below the urethrovesicle junction, which is located by gentle traction on the catheter, interrupted sutures of chromicized catgut are placed in the fascia-covered levator muscle (pubococcygeal portion) to either side of the urethra. The last suture is placed below the meatus. These sutures are tied from below upward, buttressing the posterior surface of the urethra with the musculofascial layer of suburethral tissue. The medial borders of the bulbocavernosus muscles now stand out sharply on either side of the upper half of the first row of reefing sutures. The bulbocavernosus muscles are also united in the midline with interrupted chromic catgut sutures.

Bonney sutures, which may here be called paraurethral fixation sutures, are now placed, one to either side of the urinary meatus. As before, the central portion of these sutures are placed first, to avoid injury to the urethra. The lateral parts of these sutures again transverse the bulbocavernosus muscle. In this manner the terminal portion of the urethra is supported laterally, and the mucosal edges to either side are approximated.

A fourth Bonney suture is placed posteriorly, traversing in similar fashion the mucous membrane of the vagina and that surrounding meatus. This suture is carried deep through the bulbocavernosus and pubococcygeal muscles, lateral to the suburethral reefing sutures previously inserted and tied, emerging on the vaginal mucosa. They are tied in the following order: The two lateral sutures first, then the posterior suture, and finally the anterior suture.

Finally, the remaining gaps in the vaginal mucosa below the meatus are closed with continuous or interrupted sutures of chromicized catgut. The retention catheter is left in place for forty-eight hours.

DISCUSSION

The closing mechanism of the female bladder has been investigated by several methods: dissection, x-ray, and intubation. Deductions for these studies vary as widely as the methods, and none is accepted generally. There is, therefore, no certain physiologic basis upon which the choice of operation in relative incontinence may be urged.

Natvig claims that stress incontinence is due to insufficient support on the part of the muscles and fascia surrounding the urethra. Kennedy believes in the existence of a voluntary sphincter, which may be compromised by direct injury or indirectly through distortion or fixation. Rubin, Newman and Davids state that "incontinence is probably due to incompetence of both the internal or external sphincters." Bonney and Watson assert that laxity of the anterior musculofascial sheath is responsible for stress incontinence, through a loss of the valve-like action at the angle between the urethra and bladder. Thomsen claims to have demonstrated that the closing mechanism is primarily a function of the urethra itself, and only secondarily of its surroundings, the mechanism failing when the angular bend in the urethra (Heiss's loop) is absent. Martius ascribes stress incontinence to defective sphincteric control of the urethra, and describes a lisso-sphincter and a rhabdosphincter.

It is altogether possible that bladder control may depend upon more than one factor. If this is so, incontinence could result from various types of injury and in some instances, perhaps in many, several factors may be involved at the same time. This would account for the fact that operations based on different conceptions of the mechanism of bladder control have a substantial percentage of both successes and failures. I believe that the most important elements in this operation are the two layers of suburethral sutures and the fact that more of these supporting sutures can be placed when the urethra is lengthened. It

may be argued, however, that Dudley and others have cured relative incontinence by simple elevation of the urethra, without suburethral reinforcement. Moreover, it is well known that cystocele may exist without incontinence and that urinary incontinence may actually occur after a thorough cystocele repair. It would seem, therefore, that suburethral reinforcement is not the only factor in establishing bladder control.

The operation here described has been successful in 17 out of 19 cases which have been followed for sufficient time to be properly evaluated, and appears to be successful in two more recent cases. It is upon this record, rather than on most questions of rationale, that this operation of "paraurethral fixation" for stress incontinence is presented.

I wish to express my appreciation of the fact that I was able to perform this operation upon autopsy material made available by Dr. William C. Wilentz, county physician, and upon five patients from the surgical ward services of Dr. George W. Fithian and Dr. William H. McCormick, Jr.

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THE IMMEDIATE TREATMENT OF OBSTETRIC HEMORRHAGE AND SHOCK*

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PUERPERAL mortality in the City of New York steadily declines, yet puerperal deaths from hemorrhage grow no less. In 1938 there were 357 puerperal deaths, in 97 of which, or 27 per cent, hemorrhage was an important factor. In 1939 there were 320 deaths, and 90 deaths to which hemorrhage contributed, or 35.5 per cent. In the Borough of Brooklyn, if deaths from hemorrhage are combined with those due to accidents of childbirth, as largely due to hemorrhage and shock associated with delivery, we find similar high figures, with but slight improvement in the situation; in 1938 there were 127 puerperal deaths, with 52 deaths, or 41 per cent, due to hemorrhage and shock, and in 1939 a total of 110 puerperal deaths with 42 deaths, or 38 per cent, due to these joint causes.

Our interest in this problem grows with our experience in our Brooklyn obstetric conferences, in which we inquire into the circumstances of puerperal death. Hemorrhage is the outstanding controllable factor in Brooklyn. It is common for patients to receive small amounts of blood or none at all, and in many cases transfusion is performed too late. Frequently no preparations for transfusion have been made, until evidence of shock has appeared. All the details of our 1940 deaths are not yet available for study, yet the bare facts in 6 cases assigned to

*Read at a meeting of the Brooklyn Gynecological Society, February 7, 1941.

hemorrhage, though selected at random, will illustrate the points I wish to make. All these patients were delivered in hospitals.

CASE 1.—In a primipara, aged 25 years, hemorrhage occurred two hours after forceps delivery. Two hours later, a more profuse hemorrhage was followed by shock with blood pressure 64/60. With use of ergotrate, morphine and 1,000 c.c. of dextrose she improved, and blood pressure rose to 122/66. Her condition remained good for three hours, when she died in shock.

CASE 2.—In a para iii, aged 34 years, profuse post-partum hemorrhage was treated by vaginal packing, massage of the fundus, and Trendelenburg position. One-half hour later, the pulse became rapid and thready, and her respirations were shallow, and she was given 2,000 c.c. of 5 per cent dextrose. When systolic pressure fell to 40, she was given caffeine. One hour later, 5 per cent dextrose was repeated, and 200 c.c. of whole blood given. Three cubic centimeters of coramine and 3 c.c. of adrenalin were given before death fifteen minutes later.

CASE 3.—In a para i, aged 29 years, spontaneous delivery was followed by profuse hemorrhage, and 1,000 c.c. of 5 per cent dextrose was given. One hour later another profuse hemorrhage occurred with profound shock. The vagina was packed and 1 c.c. of coramine was administered. An hour later ¼ gr. of morphine sulfate was given. Two and one-half hours after delivery, she received 750 c.c. of blood by transfusion. She did not improve, and coramine and adrenalin were given. She died in shock two hours after transfusion.

Three cases of shock following cesarean section follow:

CASE 1.—Primipara, aged 26 years, had a cesarean section after thirty-six hours of labor. Considerable hemorrhage occurred during the operation, and 3 c.c. of pituitrin were given. Shock occurred before closure of the uterine incision. Cardiac stimulants were given, 3 c.c. of adrenalin, 2 c.c. of coramine, 2 c.c. of digifoline, and 500 c.c. of 10 per cent dextrose solution. Transfusion was begun one hour after operation, and 2 c.c. of adrenalin was repeated. She died in shock shortly after transfusion.

CASE 2.—Primipara, aged 24 years, had a cesarean section after a long labor and failed version. Blood loss was estimated at 500 c.c. Shock following operation was managed with 1,000 c.c. of 5 per cent dextrose, coramine, and caffeine. Blood transfusion of 500 c.c. was given, but shock became more profound and death occurred.

CASE 3.—Para i, aged 27 years, shortly after her return to bed following elective cesarean section, suffered a profuse hemorrhage, for which she received 1,000 c.c. of 10 per cent dextrose solution. One-half hour later, bleeding recurred, and the uterus was packed. During the next half hour she bled through the pack and transfusion was attempted. She died in shock.

DISCUSSION

It is not my purpose to examine the conditions and circumstances which give rise to obstetric hemorrhage, or to discuss measures for its actual control. Knowledge of methods of prevention is fundamental, and successful management of serious hemorrhage depends largely upon the skill of the obstetrician and timely replacement of blood loss. We cannot always prevent hemorrhage, or even stop it, yet we can be prepared for it, acutely conscious of its importance as a forerunner of shock.

Every physician has seen shock follow hemorrhage; the cold, clammy skin, ashen cyanotic pallor, shallow respiration, steadily falling blood

pressure, the small rapid pulse which is finally lost, and apathy and unconsciousness just before death. This syndrome is the result of hemorrhage, yet dehydration, long labor, and anesthesia may initiate it or contribute to it, and often precipitate it when blood loss alone would not have done so.

It has been shown that large doses of barbiturates increase anoxia and so contribute to shock. In fact, all analgesics which slow labor and tend to increase the frequency of operative delivery are factors which deserve consideration. Ether particularly increases blood loss by delaying the mechanism of placental separation. The analgesia of nitrous oxide is associated with steadily increasing anoxia, and anesthesia is possible only when all oxygen has been cut out. Spinal anesthesia, if it has not affected the respiratory mechanism, invites disaster by causing vasodilatation no different from that associated with primary or neurogenic shock.

Certainly the best method of treatment of shock is prevention or at least early recognition. Low blood pressure is not an early symptom, but slight decline in the systolic level is of great significance. The pulse rate is soon accelerated, but diminution in the size of the pulse, because of diminished volume flow, is the earliest clinical sign available.

General supportive measures are important. Morphine for restlessness is valuable. Cold blood-soaked linen should be replaced by a warm dry blanket, yet enough heat to induce perspiration will defeat our purpose. Elevation of the foot of the bed at least two feet is valuable for post-partum hemorrhage, and lowering the head of the delivery table will help syncope. Hot enemas are usually not retained. Oxygen is rational for the associated anoxia, while carbon dioxide is not. Adrenalin is useless, perhaps dangerous, since the arteries are already contracted. All cardiac stimulants are contraindicated, since shock is not of cardiac origin.

Saline solution will restore blood volume if plasma loss has not been serious. It is then ineffective. Dextrose likewise passes quickly through normal capillaries. It is clear that large amounts of these fluids may accumulate in the tissues, even though edema may not be evident. These crystalloid solutions are valuable in preventing shock, but useless and perhaps dangerous when it has been established. Hypertonic solutions simply increase dehydration.

The earliest effect of uncomplicated obstetric hemorrhage on the blood is probably dilution, not concentration. Yet that follows soon enough. Whether this is so or not makes very little difference when hemorrhage occurs in the delivery room, for if blood pressure remains depressed, plasma is lost through the capillary walls. Loss of plasma is responsible for the symptoms, whether shock is due to hemorrhage or not. Delay in treatment is serious, for shock may become irreversible and neither blood nor plasma will save the patient. It is of the utmost importance to realize that danger lies less in loss of red blood cells, than loss of blood volume. It is our experience in hemorrhage that response to transfusion is prompt, while in shock it is not.

Restoration of blood volume is logical since in no other way can we maintain circulatory efficiency. Lost blood must be replaced by blood or a satisfactory substitute for blood. Transfusion is clearly indicated, yet it is common for those engaged in obstetric practice to depend upon everything else, and transfusion is not widely used. There are good reasons for this. Blood is hard to get. Professional donors for the large amounts needed are expensive, and relatives and friends have to be found before they are typed and crossmatched. Disappointments are common. We have found that preparations for transfusion take almost two hours, unless the donor is already in the hospital. Since citrated blood, because of its readiness and ease of administration, meets all the requirements of the obstetrician, blood banks are ideal, yet even they are not certain sources of supply even in large hospitals.

The result of dehydration and serious hemorrhage is loss of circulating blood volume. Unless plasma colloids are sufficient to maintain volume, aqueous solutions will not be retained in the blood stream, and their continued administration will further reduce blood volume. With reduction of blood pressure to critical levels, stasis and blood concentration occur. Then use of plasma, not cells, is indicated. Acacia, because of its colloidal properties, is far superior to crystalloids, yet it cannot be recommended unreservedly at present. In 500 c.c. of plasma, there is twice as much plasma protein as in an equal amount of blood. Red cells may be replaced later when blood is available.

Plasma or serum are ideal substitutes for blood. Simple and easy to prepare, no typing or crossmatching is necessary, and either may be given repeatedly in large amounts without fear of untoward reaction. Plasma is prepared by centrifuging citrated blood at high speed, or simply by sedimentation in a refrigerator for at least five days. Blood that is in process of settling may be shaken up and administered as blood, if of the proper type. The source is voluntary donors, and the average yield of 500 c.c. of blood to which 70 c.c. of 2.5 per cent sodium citrate has been added is well over 250 c.c. It is used with an equal amount of saline, though this is not necessary. Serum may be secured by suction by simply allowing withdrawn blood to clot; the yield is less, and it may cause an urticarial rash if it has not been pooled. Serum is clear. Plasma may be cloudy due to lipoids, fibrin veils, or precipitates which must be filtered out.

A plasma bank is practical for even the smallest hospital, while a blood bank is not. It is a convenient, quickly available fund for modern shock therapy, for plasma may be stored for a long time and be safe for use. Vacuum collection and administration is best. If tube and needle sets are properly cleansed, no reactions will be reported from its use, and autotransfusion will finally disappear from obstetric practice. Plasma cost is negligible. Those lying-in institutions without facilities for transfusion, no microscope, stale typing sera or none at all, no one in attendance able to type or crossmatch blood will soon have no excuse, for blood serum for emergencies is already commercially available.

Obstetric hemorrhage is so dangerous, so deadly, that its immediate treatment is of the utmost importance. The patient may die. Or loss

of blood, not sufficient to cause death, may predispose her to subsequent infection, from which she may die or suffer prolonged morbidity.

The role of hemorrhage in death from sepsis is an important one. We should be prepared for hemorrhage and shock before, during, and after every labor we conduct.

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SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION (WATERS' OPERATION)*

THE RESULTS IN 17 CASES

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SINCE 1824, when Physick[1] first described an extraperitoneal approach to the lower uterine segment, there have been various techniques set forth by many operators, in attempts to reduce tissue trauma and to avoid opening the peritoneum by simplifying the technique. It has been proved that peritonitis complicating this type of section, of which the Latzko was the most popular, is extremely rare. In 1940 Waters[2] described an extraperitoneal operation whereby he was able to reach the lower uterine segment by dissecting the peritoneum from the bladder fundus. His approach seemed logical, not too complicated, and he gave an excellent description of his procedure.

Recognizing the advantage of this procedure in potentially and actually infected cases where abdominal delivery was desirable, and having been disappointed by the maternal injury and frequent fetal sacrifice so commonly found in difficult forceps and hazardous version delivery of such cases, a study of this new technique was undertaken. Two years prior to this, the Latzko operation had been done in frankly infected cases, but, because of the limited exposure and the proximity of the ureter and uterine artery, difficulty was constantly encountered.

Quoting Waters "The indication for a true extraperitoneal operation is the probable or actual existence of intrauterine infection. If properly done, it should largely remove peritonitis as a cause of postoperative mortality, and at the same time it conserves the uterus." He refers, of course, to patients whose delivery by section is imperative. With this as a background 17 patients were operated upon by the supravesicular approach.

*Read at a meeting of the Pittsburgh Obstetrical and Gynecological Society, February 3, 1941.

INDICATIONS	NO. CASES
Cephalopelvic disproportion	12
Dystrophy dystocia syndrome	3
Premature rupture of membranes (18 hours' duration) and fetal distress in a diabetic with 2 previous stillborn infants	1
Pre-eclamptic toxemia with placental separation (labor 6 hours)	1

Thirteen of the 17 patients were primiparas and 4 multiparas. Three had previous laparotomies. Seven patients had ruptured membranes. Three had severe nonspecific vaginitis, one showing a luxuriant growth of condylomata acuminata around the vulva. One had a fever of 102.4° F. on admission. The average length of labor prior to delivery was seventeen hours with a range of from three to forty-three hours.

Extraperitoneal section was indicated in all but 3 cases. These 3 patients needed section because of platypelloid pelves in 2 instances and android pelvis in 1. They were not infected, were not in labor and the membranes were intact, but it was felt that to develop our technique, the performance of extraperitoneal section was justified. Their post-partum courses were uneventful except for a slight wound infection at the drainage site. They were discharged from the hospital on the twelfth, thirteenth, and thirteenth day, respectively.

OPERATIVE DIFFICULTIES

Three significant maternal operative difficulties were encountered: The first and most frequent was puncture of the peritoneum prior to extraction of the infant. This occurred in all 3 patients having low abdominal scars, and in 6 of the remaining cases. In most instances, it was possible to purse-string the peritoneal opening and prevent contamination at the time of fetal extraction, or, as in the cases previously operated upon, to do a laparotrachelotomy. As we became familiar with the technique, however, this complication was avoided.

The second was hemorrhage due to varicosities of the lower uterine segment.

The third was laceration of the bladder. This occurred in a patient who had been previously operated upon because of ectopic pregnancy and who had developed a thick keloid scar. With constant bladder drainage for eight days, the wound healed and the patient was discharged on her fourteenth post-partum day.

Four patients were delivered by low cervical section after attempting the extraperitoneal technique. Two of these 4 cases were our first attempts and the other 2 had low midline scars which made anatomic dissection impossible. Their post-partum courses were not unusual in any respect.

Because of the difficulty encountered in operating upon the 3 patients who had had previous lower abdominal operations, such scars are listed as possible contraindications to this type of operation.

POSTOPERATIVE CARE

Generally speaking, this was the same as is usually found after cesarean section. However, as most patients were hungry and peristalsis was present within twenty-four hours after operation, a full

liquid diet was given on the first day, soft on the second, and a regular diet on the third day. Neoprontosil was given intramuscularly in frankly infected cases. Blood transfusion was resorted to as needed. Most of the patients voided around the catheter on the second day and after that voluntarily. A two-day check for residual urine was routine. A gutta percha drain was placed in all wounds except 2. This was removed between the second and fourth days, depending on the amount of oozing at the time of operation and infectivity of the case.

POSTOPERATIVE COMPLICATIONS

Six patients showed no morbidity. Post-partum days averaged 16.8, with a range of from twelve to thirty-four days. The latter patient had a small gynecoid pelvis, a temperature of 102.4° F., a pulse of 140, and had been in labor twenty-one hours at the time of admission. Her convalescence was complicated by wound infection and bilateral thrombophlebitis. In 6 instances the urinary tract was infected. The substitution of a No. 16 plain catheter for a mushroom catheter and the removal of it forty-eight hours postoperatively reduced the frequency of this complication. One patient, with varicosities of the lower uterine segment, had a severe wound infection resulting in uteroabdominal fistula which closed spontaneously before discharge from the hospital. One patient, with bronchitis on admission, developed postoperative pneumonia but was discharged on the fifteenth day. Considering the type of cases operated upon, the absence of peritoneal irritation or infection is worth comment. In fact, postoperative distention was noted only once, and peristalsis was invariably present within twenty-four hours after operation.

MORTALITY

There was no maternal mortality, and no neonatal deaths. The infants ranged from 2,535 to 4,120 Gm. in weight; the former was delivered from a diabetic mother when signs of fetal distress developed eighteen hours after premature rupture of the membranes.

FINAL EXAMINATION

The results of the six weeks' follow-up were most gratifying. Of the 10 patients returning for examination only one complained of tenderness on palpation in the vesicouterine area. The parametrium was normal in 8 cases and slightly thickened in 2. The uterus was freely movable in all cases; 2 were in second-degree retroversion and one was subinvoluted. The absence of pelvic peritoneal adhesions was general.

One patient is now seven one-half months pregnant, and we plan on delivering her by low cervical section.

SUMMARY

1. In this small series of 17 cases, there was no maternal or infant mortality. Peritoneal irritation and peritonitis were absent.

2. Laceration of the peritoneum and bladder must be guarded against.

3. Follow-up examination showed only occasional thickening in the left parametrium, with the uterus always movable, usually small and forward in good position.

4. Notably lacking were the effects of trauma and infection that invariably follow difficult forceps and difficult version delivery of such cases.

5. A pre-existing lower midline scar may be a contraindication to extraperitoneal section; in which case an exclusion type of operation or laparotrachelotomy can be substituted.

6. The number and severity of post-partum complications was in direct proportion to the degree of genital infection and in indirect ratio to the operator's skill in performing this procedure.

CONCLUSIONS

The supravesical cesarean section as described by Waters offers a safe means of delivery in neglected and questionably or frankly infected cases in which a section is imperative.

We wish to express our appreciation and thanks to Dr. Charles E. Ziegler for his constant help and guidance in the selection and care of these cases.

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TWO UNUSUAL CASES OF CHORIOEPITHELIOMA*

1. A Very Young Myometrial Chorioepithelioma Four Months After a Hydatid Mole in a Primigravida of Twenty-three Years

2. An Advanced Chorioepithelioma Localized in the Cervix in a Gravida XVII of Forty-four Years With no Antecedent Hydatid Mole

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THE diagnosis of chorioepithelioma has been much facilitated since we have learned to utilize the Aschheim-Zondek test and the Friedman modification. The quantitative test has, moreover, proved particularly valuable in detecting the presence of malignant chorion at an early stage. The persistence of positive Friedman tests in instances where the uterus has been emptied of its contents whether gestational or hydatid mole suggests the presence of chorionic invasion either of the genital area or in remote places of the body. This is well demonstrated by the following case which, on account of the youth of the patient, also presented a surgical problem of unusual interest.

Case 1.—D. P. (Admission No. 397746), a 23-year-old, unmarried nullipara, was admitted to the Gynecological Service of Mt. Sinai Hospital Aug. 29, 1936, with the following history: Her menses began at 14 years of age, recurring regularly every twenty-eight days and of six days' duration, with the exception of one year (1933) when they were delayed for two to three months, accompanied by dysmenorrhea. An appendectomy in 1933 was the only operation she had undergone, following which the menses again became regular. Her last normal period occurred on March 1, 1936. She missed her regular period in April and on April 18, after a menstrual delay of two and one-half weeks, she visited her private physician who informed her that she had a retroverted uterus, which he tried to correct by passing a sound. The patient considered herself pregnant. After the instrumentation there followed

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profuse vaginal bleeding which continued until her admission May 8 to the New York Hospital. By curettage a hydatid mole was removed from the uterus. The Aschheim-Zondek test at this time was said to be negative.

Following her discharge from the hospital the vaginal bleeding continued and on June 26 she was again curetted. The Aschheim-Zondek test was positive in a dilution of 1:10. The pathologic report of the curettings was syncytioma.

Despite the last curettage, the bleeding continued. On August 10 a third curettage was performed. The Aschheim-Zondek test was positive in a dilution of 1:50. The pathologic report was chronic endometritis. Bleeding continued for a week longer, finally stopping August 19.

At the time of her admission to Mt. Sinai Hospital ten days later, the patient was entirely symptom free. Because her urine still showed a positive pregnancy test in a dilution of 1 in 20, Dr. Phineas Bernstein referred her to the hospital for further study.

The patient was well developed and well nourished. Her blood pressure was 120/80. The general physical examination was negative. The external genitalia were normal. The cervix was of normal size and consistency. The uterus was not appreciably enlarged; it was soft, retroverted, and retroflexed. The adnexa were not palpable. The parametria were negative.

The hemoglobin was 80 per cent; the sedimentation time two hours, ten minutes. The Friedman test on September 2 was positive with 1 c.c. of urine (1 in 20); 0.1 c.c. of urine was negative. This was approximately six months following her last normal menstrual period. X-ray film of the chest was negative.

Although the uterine bleeding had subsided for the past twelve days and the patient had no complaints during her observation at Mt. Sinai Hospital, the gonadotropic principle of the urine of pregnancy was present in a concentration which indicated the presence of active chorion epithelium in the genitals or in some remote place. The most common metastatic depot, the lungs, did not as yet show any lesion on the x-ray film.

The question resolved itself into two procedures: One to continue the policy of watchful waiting, and the other, surgical exploration.

As a fourth exploratory curettage in my experience would most probably again fail to disclose a small lesion which could readily escape the curette I decided to do a laparotomy and to inspect the uterus, adnexa, and adjacent viscera and, in case of doubt, to incise the uterus.

Accordingly, a laparotomy was done September 10. The findings were: an extremely soft, mottled grayish, vascular uterus which was slightly enlarged to about the size of a six weeks' gravidity. The right ovary contained a large corpus luteum cyst the size of a peach. The cyst broke in the attempt to deliver it. The left ovary was only slightly larger than normal and contained several small lutein cysts. It was adherent to the tube and the broad ligament.

Procedure.—As a preliminary step, the broad ligaments were securely clamped to minimize uterine bleeding and to prevent extension of the lesion via the lymphatics and blood stream. The fundus of the uterus and anterior uterine wall were then incised and the endometrial cavity and tubal angles examined. A positive diagnosis of chorioepithelioma could not be made on gross examination. However, the uterus was definitely abnormal. The endometrium was exceedingly friable and one small area looked suspicious. The myometrium was edematous, flabby and contracted under the examining finger. There were several small ecchymotic and hemorrhagic spots on the peritoneum, suggesting endometriosis. The uterine muscle also suggested the same abnormality. For these reasons and because of the positive pregnancy test, a supravaginal hysterectomy including bilateral salpingo-oophorectomy was performed.

Pathologic Report.—The specimen consisted of a supravaginally amputated uterus and both adnexa. Only a portion of the right ovary was attached to the specimen. The rest was received separately in fixative. Uterus appeared normal in size; measured 7.5 by 6.5 by 3.25 cm. Serosal surface was smooth. On the posterior surface near the lateral border and on the anterior surface near the lateral border, there were small superficial adhesions which had a brownish hue and resembled the tobacco-stained appearance of endometriosis. Uterus felt somewhat soft. On section the myometrium was 2 cm. in thickness, pink gray in color, rather homo-

geneous. From gross inspection at this time, there is no evidence of abnormal myometrial infiltrations. Endometrial cavity measured 5.5 by 3 cm. It had a slightly shaggy appearance, but the endometrium did not appear thickened grossly in any particular area, except in each cornu where it appeared slightly thickened. In the cervical canal about 0.5 cm. beyond the distal cut margin, a small pin point bluish area could be seen beneath the mucosa.

The left tube was normal in size, length, and configuration. Its patency could be demonstrated. Left ovary appeared slightly enlarged and measured 4.25 by 3 by 1.75 cm. A few fine adhesions were present in its inferior border. On section through the ovary, there were present small cystic follicles and one follicle cyst which measured 2.5 cm. in diameter. The wall of this cyst was somewhat hemorrhagic. At the outer pole, there was a corpus luteum which measured 1.5 cm. in all directions.

Immediately following the operation, the Friedman test was positive with 1 c.c. of urine. Six days following operation 20 c.c. of urine gave a negative Friedman test, and the same result was obtained by repeated tests throughout her stay at the hospital fifteen days after operation. The postoperative course was uneventful.

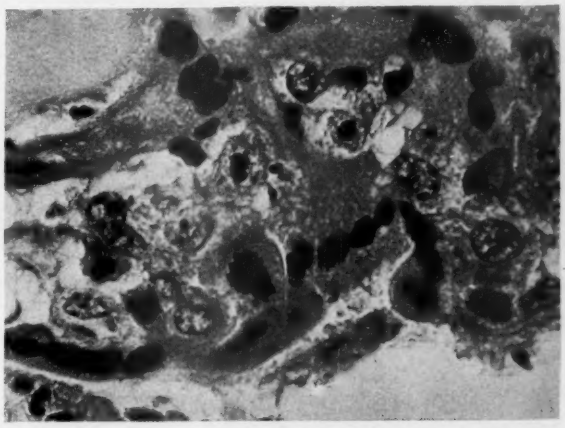

Fig. 1.—High power showing three mitoses in the center. (Case 1.)

The first pathologic report was: Chronic endometritis with hyperplasia and adenomyosis; corpus luteum cysts of the ovaries; old hemorrhage on the pelvic peritoneum. Inasmuch as the Friedman test became negative after the operation, Dr. Otani also felt that the lesion must reside in the uterus, hence he continued to make serial sections (over 200 sections) which revealed the small chorioepithelioma as shown in Fig. 1.

This patient was observed until Feb. 11, 1938, during which time the pregnancy test on urine was negative. She had had a radical mastectomy of the left breast February 1 for a carcinoma simplex which had no relationship to the original tumor.

CASE 2.—This is in marked contrast to the first. It concerns a 44-year-old woman who had 17 pregnancies, 13 of which were full-term children and 4 resulted in miscarriage. The oldest child is 25 years old, the youngest 8 years. She was brought into my office by automobile, requiring eight hours' ride from Hampton Beach, N. H., where she had had a hemorrhage five days before. She was bleeding profusely; the blood had soaked through the pads and leaked down to the floor.

A quick examination revealed the vagina filled with large blood clots and fluid blood which when cleared away exposed a dark purplish-red polypoid tumor projecting from the cervix. The vagina was tightly packed and the patient was sent to the hospital. Her hemoglobin was 68 per cent. The lesion looked like a placental polyp or possibly an extruding molar pregnancy. Under anesthesia it was possible to examine the lesion more closely. It was found to be somewhat friable and intimately adherent to the thinned-out dilated cervix which admitted the finger readily.

It occupied the entire inner circumference of the cervix, the lips of which were thinned out and at the left side presented a grayish yellow membrane about 3 × 4 mm. in thickness which covered part of the protruding mass and was intimately adherent to the cervical mucosa (Fig. 4). Part of the tumor was removed by ovum forceps; the rest of it was curetted and the membrane was excised. There was considerable bleeding during this procedure. The uterine cavity appeared to be empty except for a few small fragments which may have had some of the characteristics of the tumor lying within the cervical canal. It was my impression that these fragments were removed from near the internal os. The latter was about the width of a lead pencil. It was dilated to permit curettement. There was a sharp line of demarcation between the internal os and the tumor-bearing portion of the cervical canal.

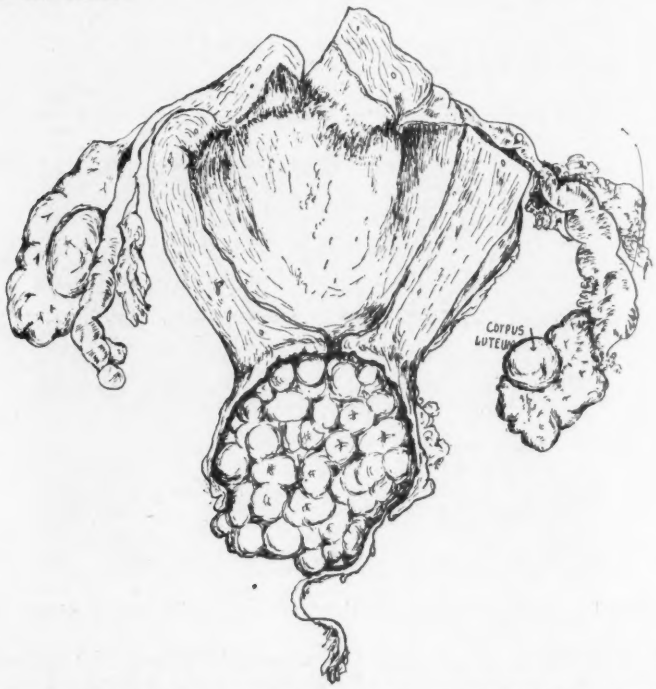

Fig. 2.—Diagrammatic sketch of uterus, showing the chorioepithelioma limited to the cervical area.

The nature of the lesion was not clear even at this stage. Its localization and its apparent origin from the cervix threw doubt upon the diagnosis of a placental polyp or of an aborting mole. Yet it resembled either of these closely. On the other hand, it was too easily removed for it to be a cervical carcinoma. There was no antecedent history of hydatid mole. Her last miscarriage at six months took place July, 1939, followed by curettage. Her periods had apparently been normal until three months preceding her present attack. After two months amenorrhea, irregular bleeding began and continued for a month. Although chorioepithelioma was considered, there were no other corroborative signs or symptoms to support this diagnosis. Only the laboratory examination of the fragments from the cervical tumor revealed the presence of chorioepithelioma. Decidua was found but no villi. An excised portion of cervix showed no significant changes.

Before the hysterectomy was carried out, a catheterized specimen of urine was sent to the laboratory for a Friedman test. Although obtained five days following the first operation, the urine did not contain the gonadotropic hormone in strengths of 5 c.c., 0.1 c.c., 0.075 c.c. and 0.005 c.c.

At the laparotomy, the uterus was found to be about the size of a five or six weeks' gravidity, purplish in color and soft. The adnexa appeared normal. There

was some induration at the parametrial bases. A typical complete hysterectomy was done with iodoform gauze drainage of the subperitoneal space. Several nodules the size of a pea to a cherry, hanging from the wall of the sigmoid, were removed. They proved to be lymph cysts.

The specimen consisted of a totally resected uterus and both adnexa received in open state. The uterus was enlarged to the size of a six weeks' gravidity and measured 12.5 by 5.5 by 4 cm. Serosal surface of the uterus was smooth and glistening. The uterus had been opened along the anterior wall. The myometrium averaged 2.5 cm. in thickness. It was generally yellowish pink and uniform in

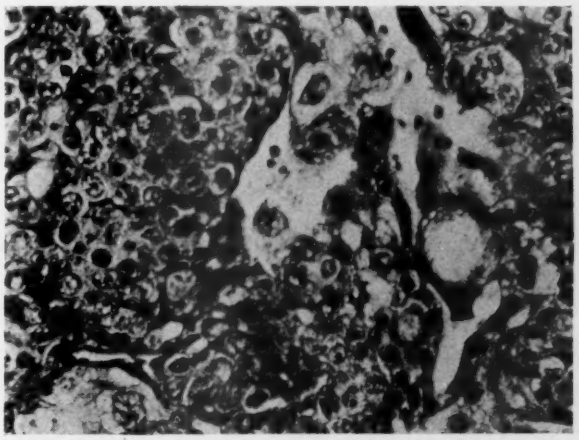

Fig. 3.—High power view of the excochleated tumor. (Case 2.)

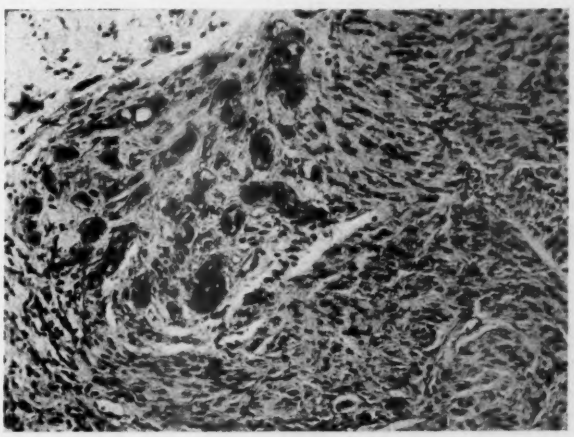

Fig. 4.—Shows syncytial giant cells from the small area near the internal os shown in Fig. 2.

appearance. There were no palpable tumors in the myometrium. The endometrial cavity measured 6 cm. from fundus to internal os and the endometrium had been largely denuded by a previous curettage. The endometrial surface was generally yellowish pink with irregular scattered superficial hemorrhagic areas. The endometrial surface was slightly roughened but no friable or necrotic masses were adherent to it. The cervical canal measured 4 cm. in length and showed a moderate distortion of the normal pattern of the arbor vitae. On the anterior wall, there was a small collection of mucus just beneath the cervical mucosa. The superficial aspect of the endocervical canal showed multiple, irregular, hemorrhagic areas

which were very superficial. There was a bridgelike area of tissue which measured 1 cm. in width and covered over a tunnel of cervical mucosa. This area was 2 cm. from the external os. There was a cuff of the portio of the cervix included with the specimen which showed no gross changes. The right ovary was normal in size. The outer surface was slightly corrugated but smooth. On section, the ovary showed a normal pinkish yellow appearance with evidence of an old corpus luteum near the outer pole. The Fallopian tube on the right side measured 10 cm. in length; fimbriated extremity was open and the lumen of the tube was patent throughout its length. The tube showed no gross abnormalities. On the left side, the ovary was approximately the same size. The outer surface likewise showed no gross abnormalities and on section the ovary had a typical yellowish pink appearance with few tiny thin-walled cysts and 2 yellowish plaquelike areas, one about the size of a pinhead and the other the size of a split pea. Received separately in fixative were 3 masses of tissue which were removed from the parametria.

The pathologic report was as follows: A small remnant of chorioepithelioma was found in the endometrium near the cervical canal (Fig. 4). The uterus otherwise showed no evidence of tumor, despite numerous sections which were made from various portions of the uterus. One ovary showed a corpus luteum. Adenomyosis of the uterus was present.

Two subsequent Friedman tests, September 19 and December 12, proved negative.

The patient was seen Jan. 14, 1941, and appears well.

SUMMARY

In the first case, the chorioepithelioma was very small and was localized in the myometrium. It occurred after a hydatid mole which resulted from the first pregnancy in an unmarried woman of 23 who two years later had her left breast removed for a carcinoma simplex. The Aschheim-Zondek test was positive in this case in a dilution of 1:50, which is not abnormally high as the gonadotropic hormone has been found in Dr. Frank's laboratory in concentrations of 0.075 and 0.05 in normal pregnancy. The Friedman test was negative five days after the removal of the uterus. This fact was significant enough to stimulate the pathologist to attempt to find the lesion which he actually discovered by making some 200 sections from the uterine wall, after the ordinary routine laboratory study had failed to reveal the lesion.

The second case was that of a woman of 44 years of age who had had 17 pregnancies (13 children and 4 miscarriages), the last pregnancy a year ago which terminated in a miscarriage. The chorioepithelioma was not preceded by a hydatid mole. It was localized to the cervix. Its origin was in all probability from the isthmus of the uterus or from the cervix at the internal os and resembled a placental mole in the process of extrusion, as both from the observation at the time of the curettage and the study of the uterus itself, no remnants were found in the uterine cavity where it is most commonly located.

I have seen several cases where the first evidence of chorioepithelioma was in the lungs and no lesion in the uterus discoverable, while in others the metastatic chorioepithelioma was located in the perineal area and vagina without any evidence in the uterus. One such case which I saw several years ago had a metastasis in the jejunum which was discovered some months later at autopsy.

As to the Aschheim-Zondek and Friedman tests, when either of these is positive, it indicates the presence in the body of active chorionic tissue. The concentration in the urine of the gonadotropic principle does not appear to depend upon the size of the tumor although an excessive amount may be assumed for highly malignant activity. In the first case, the concentration at its highest point was 1 in 50. The test appears to become negative very soon after the lesion in the genitals has been removed, indicating at the same time that no metastasis is present. A careful follow-up for an indefinite period is advisable. The diagnosis and treatment of chorioepithelioma require not only the test for the hormone of chorionic derivation but also well-established x-ray, surgical, and other laboratory technical procedures.

911 Park Avenue

RELIABILITY OF THE FISHBERG CONCENTRATION TEST IN NORMAL PREGNANCY AND THE PUERPERIUM

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THE Fishberg concentration test of kidney function is rather generally used because of its simplicity and accuracy. It has been employed for many years in this clinic in the study of the pathologic conditions of pregnancy where there is a question of lowered renal performance. It was decided to apply this test to a small group of normal women in the last trimester of pregnancy and the puerperium, in an effort to determine its dependability.

In reviewing the literature it was found that several investigators were skeptical as to the value of the concentration test of renal function in pregnancy.

Dieckmann[1] stated, "The normal pregnant woman is able to excrete urine with an average specific gravity of only 1.022 after a fifteen-hour fast." He believed this to be due to an excess amount of water in the tissues or physiologic edema. In his opinion, the low specific gravity in pregnancy is due to a decreased amount of solids, especially urea and chlorides. Stander[2] concluded that in normal pregnancy the average variation in the Mosenthal concentration test agreed fairly well with the normal nonpregnant woman, but that there were marked individual variations. In his opinion, the test was not particularly reliable. Hurwitz[3] found that several normal pregnant patients failed to concentrate urine to 1.025, although none of these individuals showed any abnormalities in the urea clearance test. Other authors, namely, Janney and Walker,[4] and Crabtree,[5] believed that water excretion in the normal pregnant woman is impaired rather markedly. On the other hand, Fishberg[6] was of the opinion that "the renal function was rarely if ever seriously impaired by the true kidney of pregnancy." He also stated that "the concentrating ability of the kidney was good."

The patients chosen for the investigation were drawn from the Obstetrical Clinic of the Henry W. Grady Memorial Hospital, White Unit, Atlanta, Georgia. This clinic is affiliated with the Emory University School of Medicine. There were 21 patients in all, and of these, all were considered to have a normal pregnancy and puerperium, with the exception of 6. The abnormal patients were included, because it is not always possible to foretell in advance whether a patient is to have a normal pregnancy or not. The Fishberg concentration test was done in accordance with accepted instructions as outlined in his textbook, *Hypertension and Nephritis*. The following is a brief description:

The patients were admitted to the hospital overnight, and their evening meal was eaten at 5 P.M. on the day before the test. This consisted of the regular hospital diet and only one glass of water or milk. No additional food or water was ingested until after the completion of the test. All specimens voided until midnight were discarded. The first specimen to be examined was obtained at 5 A.M., the second and third at 6 and 7 A.M., respectively. The patients were in bed throughout the period of examination. Fishberg[6] advised a fasting period of sixteen hours'

duration, and considered the test to be more accurate with longer periods of abstinence. It is difficult to follow this in a hospital routine, so the maximum period of concentration in this series was fourteen hours.

Fairly strict precautions were observed to forestall any break in the routine as described above. All specimens were catheterized samples to prevent any error from incompletely dried receptacles. We used a hydrometer certified by the manufacturers for urinary examinations, and checked against water on each occasion it was used. The presence of albumin was determined by Robert's reagent, but no

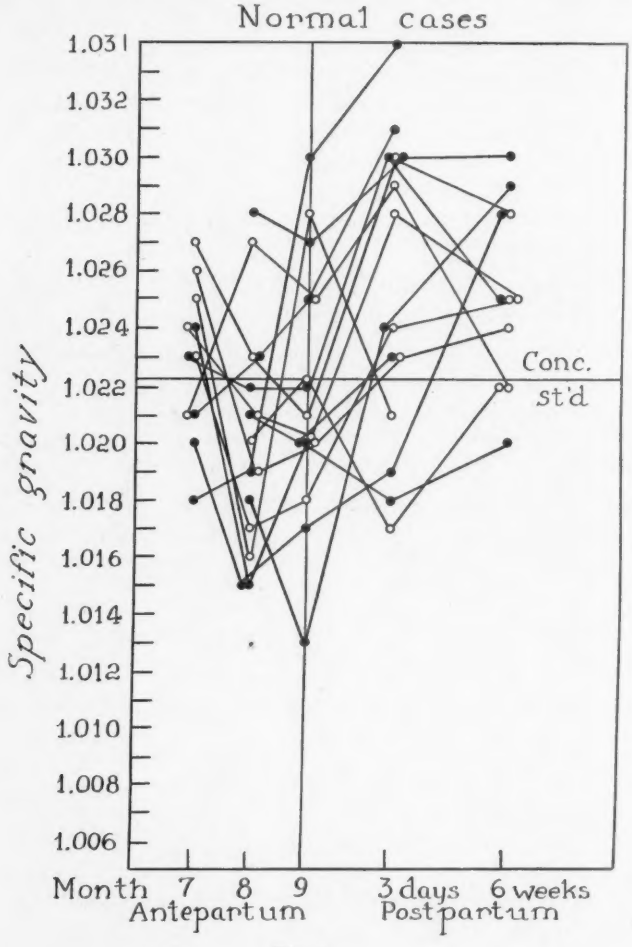

Fig. 1.

quantitative determinations were made. All tests were made on specimens which were at room temperature. The total quantity of urine was not recorded.

The heart and lungs were examined only on the first visit. A blood pressure determination and ophthalmoscopic examination were made at each ante-partum visit.

An effort was made to have the first visit coincide with the seventh month of pregnancy, the second falling in the eighth, and the third in the last month. Two postpartum examinations were made, the first three days and the second six weeks to several months post partum.

Twenty-one patients in all were studied, 14 being multiparas and the remainder primiparas. In the seventh month 15 were examined. The entire group was in-

vestigated in the eighth and the ninth months and third day post partum. Sixteen patients returned for a final examination, during a period varying from six weeks to several months post partum. All the patients were delivered of full-term infants. Of the entire group, all had a normal pregnancy and puerperium with the exception of 6 cases. These included 4 cases of mild pre-eclampsia and two cases of hypertensive disease. The classification of toxemias used is that suggested by the American Committee on Maternal Health.

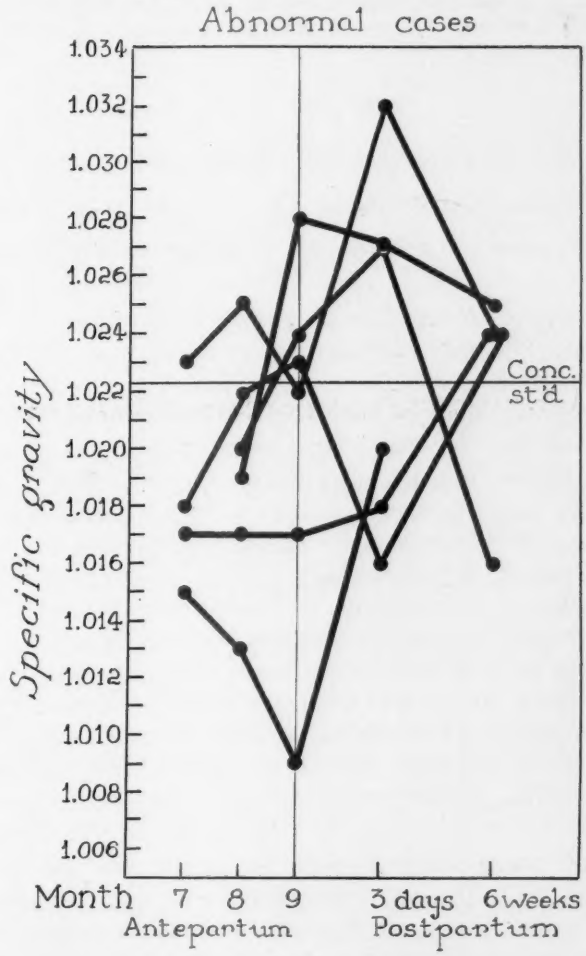

Fig. 2.

Fishberg[6] gave his standard of concentration as being normal where at least one specimen of the three had a specific gravity exceeding 1.022. It was found that in the seventh month of the 15 patients studied, 7 concentrated to this figure. In the eighth month 5, and in the ninth month 9 of the 21 patients reached this concentration level.

Three days post partum, 14 patients of the entire group concentrated as required. Six weeks to several months post partum, 12 of a total of 16 patients who returned reached the stipulated figure.

Nineteen patients of the entire 21 demonstrated a post-partum increase in their concentrating ability. Of the 2 who did not, one was a patient classified as having

hypertensive disease and the other had mild pre-eclampsia. Figs. 1 and 2 are used to show the results in both the normal and the abnormal groups.

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THE VALUE OF CONTRACEPTION IN THE CLINIC PATIENT

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IN ANY attempt to evaluate the efficacy of contraception in a group of patients, it is necessary to consider the type of patient as well as the type of contraception. In this study, all of the patients were of the low income group, most of them negroes, and some of them well below the general intellectual level of the community.

Three groups of patients were considered. The first, a group of 24 patients, were suffering with severe hypertensive cardiovascular disease, with or without renal involvement, or had been followed through repeated toxemic or eclamptic pregnancies. Further pregnancies in this group, it was felt, would be extremely hazardous to the health and life of the mother, even with the most meticulous prenatal care.

The second group of 24 control patients were followed by the Charlotte Maternity Clinic for periods averaging eighteen months. The patients received no contraceptive advice, material, or even suggestions. These patients were, or had been, equally ill, and clinically comparable to the first group. Their failure to return to the clinic following delivery accounted for the fact that no contraceptive advice was given.

The third group was comprised of 56 patients, for whom contraception was felt advisable, either for "spacing," chronic disease, or deficiency states. All of the patients, with the exception of the control group, were referred from the Charlotte Maternity Clinic to the Birth Clinic of the North Carolina State Board of Health, operated in connection with the Charlotte, N. C., Health Department. The Charlotte Maternity Clinic, operated in connection with the Duke University School of Medicine, follows approximately 800 to 900 pregnancies per year without cost to the patient. Information and material at the Birth Control Clinic is dispensed by a public health nurse, who works under the direct supervision of a group of physicians of the Health Department and the Maternity Clinic; this group decides after appropriate examination the type of and necessity for contraceptive advice. The method used by the patients in this survey is the so-called "sponge-

foam'' powder type of contraception. The technique of this method is illustrated through very explicit instructions, and accompanied by demonstrations on a plaster model. There is a small charge for the material, but if the patient is completely indigent, financial aid is available for the purchase of the powder and sponge. This technique has been used by several birth control agencies with reports of varying success.

The statistical analysis of the groups is as follows:

First group (24 hypertensive patients)		
Colored patients		23
White patients		1
No. using technique 6 mo. or more		10
No. in this group becoming pregnant while using technique		2
No. using technique occasionally		2
No. in this group becoming pregnant		1
No. not using technique		12
No. in this group becoming pregnant		6
No. on whom no worth-while follow-up was obtained		2
No. using material for period of time and stopping		1
No. in this group becoming pregnant		1
Total No. patients becoming pregnant		10
Second group (24 control hypertensive patients)		
No. patients in group		24
Total No. patients becoming pregnant		10
Third group (56 patients with chronic diseases, etc.)		
Colored patients		46
White patients		10
No. using technique 6 mo. or longer		38
No. in this group becoming pregnant while using method		9
No. using technique occasionally		4
No. in this group becoming pregnant		4
No. not using technique		10
No. in this group becoming pregnant		5
No. using material for period of time and stopping		16
No. in this group becoming pregnant		10
Total No. patients becoming pregnant		28
Totals of the first and third groups:		
No. patients referred	80	
Colored patients	69	
White patients	11	
Total No. patients becoming pregnant	38	
Or 40 per cent of referrals.		
Total No. patients using method 6 mo. or longer		48
No. in this group becoming pregnant during this period		10
Or 20 plus per cent effectiveness of the method.		

In the discussion of the above analysis, it must be pointed out that the cases were not in any way selected, other than as stated. The totals represent all of the patients referred from the maternity clinic to the birth control clinic, on whom any follow-up could be obtained; a period of time slightly in excess of three years that was covered by the study. Accurate and appreciably worth-while follow-up of any of the patients was difficult but only rarely impossible. The patients in the first and second groups were or had been seriously ill, and had exhibited extensive disorders of the vasomotor and allied systems to such a degree that they were classified as pre-eclamptic, eclamptic, or hypertensive individuals.

This group of patients had undergone from one to ten previous pregnancies, with an average of four. Their ages were from seventeen to thirty-seven, with an average of twenty-six. The group of 56 patients referred for chronic disease, "spacing," etc., had experienced from 1 to 15 pregnancies prior to their referral, with an average of 5. They ranged in age from seventeen to forty-one, with an average of twenty-eight.

The technique advised and demonstrated is perhaps the most simple, economical, and suitable for this type of patient of any known at present. In no case was there any difficulty in comprehending the technique or procuring the material. None of the patients desired further pregnancies. The various reasons for discontinuing or not employing the contraceptive methods were "too much trouble," "husband dislikes the idea," or no reason at all. It was apparent, however, that the individuals were not sufficiently interested to carry out any contraception for any length of time.

The hypertensive group represents definite potential mortality or morbidity for subsequent pregnancies, and the burden is on the clinic to prevent these pregnancies from occurring. A return of almost one-half of these patients in a pregnant state, usually in the late middle or last trimester, is a definite factor in the continued high mortality in the hypertensive individual.

Corbet, R. M.: A Visit to Certain North American Clinics, Irish J. M. Sc., p. 59, February, 1940.

A tour was organized by the Gynaecological Club of Great Britain and Eire at the invitation of the Gynaecological Travelling Club of North America which had visited Great Britain in 1934. There were ten members on the tour. Between August 27 and September 18, 1939, they had visited Montreal, Toronto, Ann Arbor, Chicago, Washington, D. C., Baltimore, Philadelphia, New York, and Boston.

There is no doubt that America is years ahead in organization, method, and thoroughness of investigation. It appears more than probable that a certain amount of this investigation is overdone and represents a wasted effort, except that it keeps their staffs employed. On the other hand, the preoperative investigation of the gynecologic patient must be of benefit. In all, it reduces itself to a question of expense, as these hospitals are enormously costly and the nonmedical people to whom we talked complained of the cost of illness.

There was comparatively little midwifery seen, as cases will not occur according to plan, but they did not seem to err on the side of conservatism. It is impossible to compare the morbidity rates, as the standards varied. In general, their criteria are more stringent than ours, four-hourly charts being the rule rather than the exception. In operative gynecology, we were most struck by the expert manner in which vaginal hysterectomies were performed. Their operations for the cure of prolapse, where no hysterectomy was done, often seemed inadequate. While they were willing to remove the whole uterus by the vaginal route, there appeared to be a very general reluctance to perform total abdominal hysterectomy. In at least half a dozen cases the cervix was so infected that it had to be cauterized or otherwise treated from below, and then the abdomen was opened and subtotal hysterectomy performed.

WILLIAM C. HENSKE.

Special Article

MODELS, MANIKINS, AND MUSEUMS FOR OBSTETRICS AND GYNECOLOGY*

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NATURAL history is taught with striking success in three dimensions, in natural sizes, and in normal colors. Anatomy can, for the most part, only be taught adequately in actual proportions in three dimensions. Mechanisms of delivery and steps of operation can only thus be clearly visualized. Drawings and movies are makeshifts. The tortuous trip of the fetal skull through the winding pelvic tunnel, and the enforced moulding of ball into egg cannot otherwise be demonstrated. The attempt to teach students forceps extraction or podalic version except on a manikin is pedagogic malpractice. To utilize the living woman as a first step forward familiarizing the student with the finger tip findings of early pregnancy, of retroversion, or of reposition, when this can be done on a lifelike model, is not alone callous and unwarrantable, but the clinic opportunities are limited and inadequate; the tempo hurried.

Apropos of insufficiency of material, pelvic structure such as muscular and fascial planes and vessels and relations of organs will have to be taught with models as long as present conditions persist. The proportion of female cadavers available for dissection of the reproductive organs runs, I am told, to less than 5 per cent of the bodies obtained from the morgue. Moreover, these are chiefly of old women with atrophic tissues. In trying to find pelvic floors to dissect in order to make a new series of accurate and low-priced models for our obstetric-gynecologic museums, I am actually having to apply to several universities.

Most operations are on a scale such that no more than one onlooker on each side of the operator, in addition to the assistants, can observe the details. All manipulations inside the abdominal cavity or up the vaginal canal are out of sight, except with large tumors or considerable prolapse. Only cesarean section or big fibroids can be shown to a section or a class. In teaching the anatomy or the stage of the operation each student, undergraduate or postgraduate, should have in his own hands the model of the structure. One model to pass around the class can never synchronize with the words of the instructor.

All this is illustrative of the point I am trying to drive home. This is that we must have models in such number that they are not merely shelf exhibits, but hand-to-hand pieces. Therefore each must be light in weight, strong in material, and cheap in price. One of the best examples of what I mean is an actual experience from my own teaching. A sculptor who later became famous and actually wealthy, could not pay for his first masterpiece, namely, the dimpled pink model he and

*Read at a meeting of the New York Obstetrical Society, February 11, 1941, with exhibit of birth series and pelvic teaching series.

his wife created. So I gave him a receipt in full after he had made me a pelvis and a fetal skull, exactly half life size. This pair of models, cast in quantity in reinforced plaster, could be sold to my students for a quarter. They learned fontanels, flexion, rotation, and position, each with his own in his hands. This plan I am now reviving, hoping, moreover, to put both pelvis and head into a slightly flexible form, so that the pelvic cavity can be compressed to show a funnel shape, and the inlet made oval or flat or oblique, then jump back to gynecoid; and the head allow for molding by hand pressure.

Here is a second revival—again, after a half century. To teach repair of birth injuries to the pelvic floor, I provided the students with models of cheap flexible material, lifesize, showing at least two varieties of laceration, for suturing. The tear can be drawn open to demonstrate the different planes or the jagged character of the damage, the depth and distance up the posterior or lateral vaginal wall. Layer stitching is feasible. Demonstration of too shallow bite or defective apposition is facile. Gelatin and not living structure pays the penalty of mistakes and fumbling.

Of the pelvic teaching models in rubber this is the first demonstration. These models are for familiarizing the student with bimanual palpation of normal and other findings. The compressibility of the isthmus in early pregnancy cannot often be found in the outpatient department for demonstration. Here is a manual training which allows time for persistence until the eye in the finger tip gets real acuteness. It is a skill we of the last century *had* to possess, and we want the new generation of students to develop it fully again.

For instruction in placing the diaphragm in contraceptive clinics, a model is found very welcome to patients in order to demonstrate the location of the diaphragm when in proper place, both reaching behind the projecting cervix and also tucked under the bony arch in front. It shows the patient that nothing can escape upward. A second model is a vulva with the vagina of a shape to accommodate the circular pessary, and it is provided with a window in the anterior vaginal wall. This serves two purposes. All patients are taught to recognize the feel of the cervix, first without cover, and, second, after the rubber of the dome of the diaphragm is over the projection. With this model she can see her finger tip touch the cervix. Then she slips in the compressed circle, which she can watch as it either passes the cervix or stops against it. Once it is expanded in proper place, her finger palpates the covered cervix. It then crooks forward to make sure the anterior rim of the device is hooked in under the pubic arch. If her finger tip is unable to touch the protected "mouth of the womb" which is right under her eyes, she can have confidence he cannot either.

Furthermore, there are, in these days, certain patients given to asking questions. And more and more they are becoming better and better satisfied if they are given an explanation adjusted to their particular capacities. The simplest answer, whenever any demonstration is thought desirable, is of course, the diagram, preferably of life size. Where only the roundness of organs can explain the matter, then a finished type of illustration is needed. Where actual comprehension of the replacement of a retroversion, or where there is a tumor or a prolapse to be visualized, then the model, this flexible model, comes into its own. I have known an intelligent woman persuaded on the instant to have treatment or operation, because she could grasp the idea readily, when she otherwise

would have had to hark back to her mother's or grandmother's mental state—the time when, if The Doctor said so, that was all there was to it.

The "Birth Series," sculpture of the stages of labor, has already been described in the October issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, but it has never been presented as part of a medical program. Again I draw attention to the very elaborate research among the roentgenograms of six large series which were milked to get this detail. These are not the cadaver obstetrics of the picturing of the textbooks. This is life in action, life arriving, tense and not collapsed. The x-ray film now delineates soft parts. As examples of its records, delivery on the x-ray table gives us this extraordinary lift of the external os nearly out of the inlet, and this thinness of uterine wall.

Two new models that are rather complex have just been added to the series.

"Birth Prelude," the three-foot disc of the ten intrauterine months, and "Birth Relief," the ten-panel half-size group, have been pictured in the JOURNAL in October. My present business with all these is to reproduce them in a material which is light and not fragile, to meet the demand for travel to exhibits on the part of state health boards and maternity centers. Plaster is right for museums only.

The baby shown in the models is in two forms. One is after regaining of birth weight, of average dimensions and weight, in flexible rubber composition, eventually to be articulated. The other is the toy or doll, issued in this form in order to test the wearing qualities of various compositions of rubber by the hard usage of the playroom. The distinguished sculptor, Miss Malvina Hoffman, has visited our maternity nurseries to make this original, and as author of the book, *Sculpture Inside and Out*, has put her special knowledge, as well as her great skill, on the problem of furnishing us with a manikin, perfect for teaching as well as a beautiful example of form. The toy purposely lacks flexibility and play of joints, and the fontanels and molding quality which are being studied.

Drs. Caldwell and Moloy have cooperated with Miss Hoffman, Mr. Belskie and myself, and Dr. J. B. Truslow, in trying to work out types of pelvis. These can eventually be furnished in a rubber compound, mounted on a stand, at a price less than the bony pelves that are usually compounds of more than one type. Dr. Moloy shows samples of types. The remarkable demonstration of passage in relation to passenger from reconstruction by stereoscopy and from molds taken from the newborn head, is a conspicuous forward step.

The Museum which every department of obstetrics and gynecology should have needs three quite different forms. One is the single specimen, which can be an actual embryo or uterus or a wax model, or a reproduction from a cancer of the breast like the beautiful series of Bulbulian from the Mayo Clinic. Second comes the multiple form, for the shelves of each school, things which every department in our line needs to refer to, especially if the specimen or growth is a little unusual, so that it cannot be readily gotten for demonstration at the time of its appearance in the course. Third, is the teaching kit, such as we have been describing, for actual handling by the student, also multiple. Here the steps of operation can be in panel form, and compact in relatively small area.

The specimen of the future will not be in glass, suspended in fluid, but bedded in transparent plastic, permanently preserved in convenient form for close inspection, and thus easily passed from hand to hand.

As to color, we find that the models for medical teaching are best in full natural color, but that those in which colleges and schools show keen interest, such as the embryology and delivery series, need show form only. Here, the terra cotta tint advised by Malvina Hoffman is acceptable, with shading or lightening for special areas or membranes.

Our craftmanship that is busied with the intricate and delicate mechanisms of the reproductive system can thus make use of all the aids now developed in educational advances and in shop instruction and in anthropology and in museum techniques.

Hudson, F. I.: The Midwife Problem, Delaware State M. J. **12**: 176, 1940.

To provide good health service to mothers who desire midwife service, a health department should: train, supervise, and register all midwives; provide satisfactory prenatal service for all midwife cases or see that such service is provided by other agencies, and make provision that each new accoucheuse must have certain qualifications of training and experience before formal registration.

According to the author, in 1930 there were 157 midwives in Delaware; 106 of these were colored and 51 were white. In 1940 only 76 midwives were registered; 20 of these were white, and 56 were colored.

In 1929, 19 per cent of all babies in the state were delivered by midwives. In that year the infant mortality rate was 82 per 1,000 live births. In 1939, 12 per cent of all births were delivered by midwives, and the infant mortality rate was 43 per 1,000 live births.

Much has been accomplished in Delaware by providing midwife classes at regular intervals. Good instruction in the form of demonstrations has proved the best method. Didactic lectures are practically useless, since most of the words used are out of the range of the average midwife's vocabulary.

J. P. GREENHILL.

Klumpp and Weilerstein: Sulfapyridine—Is It a Safe Drug? M. Ann. District of Columbia **9**: 83, 1940.

Under the Food, Drug and Cosmetic Act traffic in new drugs is prohibited unless such drugs have been adequately tested, and the Secretary of Agriculture must satisfy himself that the drug is safe before permitting the application for sale to become effective. In order to do this the manufacturers were contacted, and it was learned that about 280 physicians or investigators had received consignments of the drug for experimental use before January 25, 1939. Approximately 100 were justified in expressing an opinion, and their combined experiences represent knowledge gained from more than 2,000 cases of pneumococcal pneumonia in human beings.

It was the consensus of opinion that the therapeutic use of the drug was accompanied by certain untoward effects, and these were in their general nature similar to those encountered in the use of sulfanilamide. It is significant that there was no death directly attributable to the drug in the series of cases investigated. It is seen from the table listing the toxic manifestations that nausea occurred in 36 per cent and severe vomiting in 12 per cent of the cases reported. Dizziness, cyanosis, renal symptoms, and fever occurred in the order listed.

In answering the question, "Is sulfapyridine a safe drug?" the authors say that it seems to be.

J. P. GREENHILL.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

THE SALVAGE OF FETUSES IN GRAVIDIC TOXEMIAS*

A STATISTICAL STUDY

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THIS study is the analysis of the stillbirths in toxemic patients that occurred in Philadelphia in the first fifteen months of investigation by the Stillbirth Committee under the auspices of the Obstetrical Society of Philadelphia, with Dr. Thaddeus L. Montgomery as Chairman.

Toxemia was the most frequent known cause of these stillbirths. There were 45,750 total deliveries during the period from Oct. 1, 1937, to March 31, 1939, in Philadelphia. There were 1,024 stillbirths of twenty or more weeks' gestation. Toxemia was considered as a primary factor in 137 cases, and as a contributory factor in 41 cases.

The toxemic stillbirths were studied as suggested by Dunham, Tandy and associates[1] in relation to:

1. Whether the fetal death occurred before the onset of labor,
2. The period of gestation at which stillbirth occurred,
3. The method of delivery,
4. The frequency of certain complications of pregnancy and labor associated in this study with gravidic toxemias.[1]

The complications of toxemic pregnancies were studied in relation to whether the committee regarded the condition as the primary or secondary factor in the toxemic stillbirth.

Table I shows that 75.18 per cent of the toxemic stillbirths occurred in the antenatal period, while only 18.97 per cent occurred in the intranatal period, and 5.83 per cent were not recorded.

TABLE I. TIME OF FETAL DEATH IN GRAVIDIC TOXEMIA WITH RESPECT TO LABOR AND PERIOD OF GESTATION

PERIOD OF GESTATION WEEKS	ANTENATAL		INTRANATAL		NOT RECORDED	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
20 to 27	22	88.0	3	12.0	0	–
28 to 35	38	76.0	12	24.0	0	–
36 or more	43	79.63	11	20.37	0	–
Total	103	75.18	26	18.97	8	5.83

These figures compared with the general stillbirth rate as illustrated in Table II, show a greater proportion of deaths in the thirty-six or more weeks' gestation period. There is likewise an increase in percentage of antenatal deaths over that of the general stillbirth level during *any* time of the gestational period, but nothing

*Read at a meeting of the Obstetrical Society of Philadelphia, December 5, 1940.

TABLE II. TIME OF FETAL DEATH WITH RESPECT TO LABOR BY PERIOD OF GESTATION*

These Figures Include Stillbirths From All Causes.

WEEKS OF GESTATION	TOTAL	DIED BEFORE LABOR		DIED DURING LABOR	
		NO.	PER CENT	NO.	PER CENT
	6,367	3,713	58.32	2,654	41.68
20-27	1,084	840	77.49	244	22.51
28-35	1,756	1,298	73.92	458	26.08
36 or more	3,478	1,542	44.34	1,936	55.66
Not reported	49	33	----	16	----

*Taken from: Am. J. Public Health, p. 494, 1938.[1]

to compare with the greater percentage increase during the thirty-six or more weeks' period of gestation. Of these 137 cases of primary toxemic stillbirths, 84 had received adequate prenatal care while 35 had received inadequate care. There was no record of the type of prenatal care given in 8 cases, while in 10 instances they had no prenatal care whatever.

In reviewing the 22 cases of the antenatal fetal deaths of twenty to twenty-eight weeks, I found that 6 had inadequate prenatal care, 11 had adequate care, and 3 had no prenatal care, while 2 cases had no notation on the record. The Committee classified 21 of these cases as nonpreventable, while the remaining one was classified as the patient's failure to comply with the advice of her physician.

In the group of fetuses that died antenatally between the twenty-eighth and thirty-fifth week, there were 38 cases. Twenty-seven mothers had adequate prenatal care, 7 had inadequate care, 2 had no prenatal care, and in 1 case, there was no notation whatever. Of these 38 cases, 21 fetuses were macerated, 10 were not macerated, and there was no record in 7 instances. Of the 10 fetuses that were not macerated, only 3 mothers had had analgesia and no operative interference, and these 3 cases were considered nonpreventable by the committee.

If we try to find some causative factor for the stillbirths, and review several cases of nonmacerated fetuses with a view of fetal salvage, we find:

First (No. 96) a 28-year-old white girl, primiparous, private patient, with a previous gall bladder history, who had adequate prenatal care. Her labor of eighteen hours was associated with uterine inertia. She had eclampsia at thirty-nine weeks' gestation. She had a rectal analgesia and a low forceps delivery. The fetus was not weighed but was not macerated. This mother died. Now I feel that more efforts should have been made in treating the hypertension, rather than hurrying to deliver. This case was classified as nonpreventable.

In another case (No. 695) a twenty-five-year-old, white, private, primiparous patient with adequate prenatal care died after being delivered spontaneously with no analgesia nor operative interference at the thirty-fourth week. This death was ascribed to an error in judgment on the part of the physician.

There were 3 cases where the fetus was not macerated, and after due study, were ascribed directly to the patients for their refusal to comply with the advice of the physician.

The remaining cases of this antenatal twenty-eighth- to thirty-fifth-week group were judged as nonpreventable.

In analyzing the 43 instances which occurred during the thirty-sixth week or more of gestation in antenatal toxemic stillbirths, we find:

Twenty-seven mothers had what was considered adequate prenatal care, 10 were considered inadequate; 2 had no prenatal care whatever, and no notation was made in 3 instances.

Five mothers of these 43 cases died; 2 had had adequate prenatal care and 1 had no prenatal care. The women who died left 18 living children; they were all charity cases. Four were colored and one was white.

There were 26 macerated fetuses; 14 were not macerated and there was no record in 3 instances.

Of the 3 cases where the death of the fetus occurred intranatally from the twentieth to twenty-eighth week, only one had adequate prenatal care. These were classified as nonpreventable.

Among the 12 instances of intranatal deaths at the twenty-eighth to thirty-fifth week (it is during this period that fetuses are generally heavy enough to save, unless some abnormal placental development is present), we find:

Only one case was classified as ascribable to an error in judgment on the part of the physician. Another case was classified as ascribable to the patient. The remaining supposedly nonpreventable deaths demand scrutinizing.

CASE 700.—This case occurred in a 37-year-old, white, private, hypothyroid primipara (basal metabolic rate −20) with a history of impaired renal functions and adequate prenatal care. Her labor went seventy-two to seventy-five hours after a surgical induction by rupturing the membranes. As labor progressed the fetal heart was not heard; then 2 doses of morphine sulphate and 2 doses of sodium amytal were given. After the long labor with the patient showing signs of exhaustion, the floating head was grasped with forceps through an undilated cervix under ether anesthesia, and was delivered. The length of gestation was thirty-two weeks. The fetus was not macerated and weighed 1,474 Gm. Pathologic report was birth trauma; no pathology of cord or placenta was noted.

CASE 72.—Another patient, a 38-year-old, white, private multipara had no prenatal care. She was delivered by accouchement forcé internal podalic version after the membranes had been ruptured surgically. She had a labor of eighteen hours, during which time she had 5 convulsions. Intravenous sodium amytal was used as a narcotic agent. This occurred at the thirty-second week. The fetus weighed 2,289 Gm. and was not macerated. This mother died eighteen hours after delivery.

In analyzing the 11 cases of stillbirth of gravidic toxemias during the intranatal period of thirty-six weeks' or more gestation, very enlightening information is obtained. Here are a few cases:

CASE 793.—One patient was admitted to the hospital in convulsions. She had no prenatal care, and was delivered with outlet forceps. The patient died of a ruptured heart.

CASE 513.—Another patient under private care for albuminuria, casts and hypertension, had adequate prenatal care. During a fourteen-hour labor at the fortieth week, she received castor oil, quinine, pituitrin, surgical rupture of the membranes, morphine, scopolamine, atropine, rectal ether, and paraldehyde. She was finally delivered by the second set of forceps.

Another patient having symptoms of toxemia, during the last two months had received so-called adequate prenatal care, was allowed to have a labor of sixty-eight hours. During the labor she received castor oil, pituitary extract, morphine, scopolamine, Gwathmey's rectal ether, and magnesium sulphate. She was finally delivered by low forceps at her fortieth week of a fetus weighing 3,104 Gm. This patient died.

CASE 115H.—Another patient with a history of diabetes, hypertension, obesity, and having inadequate prenatal care, was allowed to deliver spontaneously at home in the thirty-sixth week of a very large strangulated baby which was not weighed. This is a glaring example of the need of education not only of the laity, but of some physicians who undertake the responsibility of delivering at home.

Table III shows the infrequency of the operative procedures associated with this complication of pregnancy and especially the percentage of intranatal deaths that are associated with operative interference.

There were 4 cases of cesarean section where the fetus died before delivery. Three were performed in the twenty- to twenty-eight-week group. The fourth (No. 46) was performed at the fortieth week in a forty-year-old white, charity multipara who had had two previous stillbirths. She had had adequate prenatal care. Hysterotomy was done when eye changes were noted and a nonmacerated fetus, weighing 1,502 Gm., was delivered. This was classified as being nonpreventable.

This table shows but two instances where low forceps and midpelvic forceps applications were performed and intranatal deaths recorded. There were two instances of breech extraction performed during toxemic labor, resulting in stillbirths. Version and extraction were done on only one occasion. There were no instances of cesarean section during this period of investigation which resulted in an intranatal stillbirth.

Primary toxemic stillbirths, totaling 137 cases in the first 1,024 stillbirths, were complicated by twin births in three instances. Of these 3, one went to twenty-nine weeks' gestation with adequate prenatal care and was delivered spontaneously of macerated fetuses. Another had thyroid disease complicating the toxemia. She was given adequate prenatal care but was allowed to progress until the thirty-eighth week before medical and surgical inductions were done. In this case, the first fetus was a breech, delivered spontaneously; while the second fetus (a cephalic presentation) was alive when spontaneously delivered. The third set of twins was delivered spontaneously at the thirty-ninth week by a patient with a history of mild toxemia. Death of the fetuses resulted from inadequate prenatal care, either due to the patient herself or to improper guidance by the physician. These fetuses weighed 2,428 and 3,175 Gm. According to the committee, this was classified as nonpreventable.

TABLE III. TIME OF FETAL DEATH WITH RESPECT TO TYPE OF DELIVERY

TYPE OF DELIVERY	ANTENATAL DEATHS		INTRANATAL DEATHS	
	NO.	PER CENT	NO.	PER CENT
Spontaneous	90	65.69	18	13.13
Low forceps	7	5.10	2	1.45
Midforceps	1	0.72	2	1.45
Cesarean section	4	2.91	0	–
Breech extraction	6	4.36	2	1.45
Version and extraction	4	2.91	1	0.72

Table IV shows that only in six instances was the fetal death due to birth injuries as noted on the reporting charts, and of these only two were classified as nonpreventable.

Prolapsed cord was noted twice; placental infarcts and necrosis were a contributory factor in three cases, and these were all considered as nonpreventable by the Committee.

The case of syphilis complicating toxemia was classified as nonpreventable.

It is interesting to note that placenta previa, a condition obviously nonpreventable and admittedly one in which fetal death is likely to occur, took place only twice in this group of toxemic patients.

There were 92 cases of premature placental separation during the period of study, of which 27 cases occurred in toxemia patients. Here one is absolutely and immediately confronted with the need for further study of the placenta and its relation to gravidic toxemias. There was no question of the management of any of these cases, as they were classified as nonpreventable. I feel that some of the fetuses could have been saved if we knew more of the placenta, cord, and envelopes and their relationship to this complication of pregnancy with toxemia.

Of these 27 cases of premature separation complicating labor, the fetus died antenatally in 16 and intranatally in 8 instances. There was no notation in 3 cases. This complication occurred as early as the twenty-seventh and as late as the fortieth week. There were 9 instances where hysterotomy was done; 12 were delivered spontaneously; there was one breech decomposition; one podalic version; and one case where aftercoming head forceps were used. There was one midforceps application and two low forceps applications, one of which was complicated by impacted shoulders. Of these placental separations, if the patients were immediately hospitalized and studied, although condition is more difficult to control, some reduction may have been effected.

Another factor to be seriously studied is the problem of prematurity and immaturity. It was noted that the weights of the fetuses in the various periods of gestation varied greatly in each group. Table V suggests the possibility of the co-existence of *both prematurity and immaturity.* While the rate of infantile mortality is not difficult to establish, it is quite another matter to determine the rate of immature babies. While the term immature suggests an entirely different condition from that which is indicated by the term premature, the two have often been used synonymously to express the state of debility of the newborn infant due to an incomplete development of the organism.

TABLE IV. TIME OF FETAL DEATH WITH RESPECT TO WEIGHT AND CONTRIBUTORY MATERNAL CAUSES COMPLICATING TOXEMIA

CONTRIBUTORY MATERNAL CAUSES	NUMBER OF CASES	– TO 1,000		1,000-1,500		1,500-2,500				2,500 AND OVER			NO RECORD
		28-35 WEEKS		28-35 WEEKS		ANTENATAL		INTRANATAL		ANTENATAL		INTRA-NATAL	
		ANTE-NATAL	INTRA-NATAL	ANTE-NATAL	INTRA-NATAL	28-35 WEEKS	36 –	28-35 WEEKS	36 –	28-35 WEEKS	36 –	36 –	
Syphilis	1					1							
Prolapsed cord	2	1											1
Placenta previa	2					1					1		
Placental infarcts and necrosis	3	1				1							1
Birth injuries	6											6	
Premature separation	27	1	3	1		4	2	2		1	4	2	7

TABLE V. THE WEIGHTS OF FETUSES OF PRIMARY TOXEMIC STILLBIRTHS

WEEKS OF GESTATION	NOT RECORDED	– TO 400	400 TO 1,000	1,000 TO 1,500	1,500 TO 2,500	2,500 TO 4,500
20-22	2	1	1	0	0	0
22-28	10	0	12	4	3	1
28-37	16	0	6	10	21	10
37-43	6	0	0	0	7	22
Not recorded	4	0	0	0	0	0

Toxicosis is one of the most important causes of premature births, being outnumbered possibly only by twin pregnancies. Of course, syphilis and polyhydramnios are also important factors. There is no doubt that children born of women suffering from eclampsia, grave hypertension, and albuminuria show a greatly retarded development. When comparing the children of eclamptic patients with children delivered during the same gestation period, we find that they continue to present the fetal characteristics with a meager chest development that contrasts with the less relative size of the head, even though it remains dominantly large, and especially the abdomen with its absence of the panniculus adiposus.

If we consider these neonatal births simply as weaklings and later capable of having a normal development, we should equally remember the percentage that die in the first few days or weeks of life, as compared with births of nontoxemic mothers in the same gestation period.

This paper would not be complete without calling to attention the relationship of the type of operative delivery, the anesthetic agents used, the management of the toxic patient immediately before the procedure, upon the immature, premature, and toxic fetus. Schreiber,[2] in his study of apnea of the newborn and associated cerebral injury, shows the effect of anesthesia, analgesia, oxytocics, operative, normal birth trauma on the respiratory center with a resultant cerebral anoxemia with or without irreparable brain damage on an apparently healthy full-developed fetus. If this is so, what would be the effect of all these factors on a fetus that is already handicapped with the toxic factor superimposed on a premature immature fetus?

Apnea is commonly found in a higher percentage in toxemic babies born alive, but when the mother has been given analgesic and anesthetic agents over and above the pharmacologic doses recommended (whether a necessity or not) the dose may be enough to spell the difference between a live or dead fetus.

My personal opinion is that in increasing the salvage of fetuses of toxemic mothers, we will be increasing at the same time the neonatal death rate, but that this increase will probably only be about one-third or one-half of the number of fetuses saved.

The complexity of the data-examined documents implies how unpropitious are the repercussions of the gravidic toxemias.

COMMENT

There was an increase of the number of toxemic stillbirths antenatally over the general stillbirth rate, and more especially after the thirty-sixth week. This brings into bold relief the absolute necessity for adequate *intelligent* prenatal care.

The average age of all these toxemic patients was 28.41 years.

In review of the 6 cases of birth trauma associated with toxemia, it was interesting to find that the average age of these patients was 35.6 years. Four of these were multiparas and 2 were primiparas.

I feel that hysterotomy has a very limited place in the treatment of toxemia. Excepting for actual indications, such as complicating hemorrhage, disproportion, abnormal presentation, etc., the following conditions should be fulfilled before considering cesarean section:

1. Pregnancy should be over twenty-eight weeks.
2. Evidence of fetal life.
3. Lapse of several hours from the time of administration of narcotics and analgesics.

4. Active treatment of *toxemia*, not simply hypertension, for a reasonable length of time in a hospital.

5. Obstetric consultation.

A glance at the case reports definitely shows the importance of education of patients and education of general practitioners who do obstetrics in not waiting too long before seeking obstetric advice in the management of toxemic patients. The importance of actively treating the toxemia, not simply hypertension, and, if no improvement is noted, or if the toxemia increases in severity, the advisability of induction of labor is certainly borne out. Labor then should be induced medically, and only surgically if necessary, during a period when the fetus is free from possible effects of narcotic agents.

A study of the cases of intranatal stillbirths showed that as a rule:

1. Interference came too late.

2. Effect of narcotics, analgesics, and anesthetics was not too seriously considered.

During the same period, there were 92 cases of premature separation, 27 of which were associated with toxemia.

There were so few autopsies done on these fetuses that deductions could not be drawn.

SUMMARY

1. An analysis of 137 toxemic stillbirths complicating the first 1,024 cases of stillbirth studied by the Philadelphia Committee from Oct. 1, 1937, to March 31, 1939 are reported. During that period, there were 45,750 total deliveries.

2. Evidence is given showing an increase in the antenatal deaths of the toxemic fetuses during any time of the gestational period as compared with the general stillbirth level.

3. The greatest increase of the percentage of antenatal deaths of the toxemic fetuses occurred in the thirty-six or more weeks' gestation period.

4. There are still a great number of patients with inadequate prenatal care, notwithstanding the education in this respect.

5. There is lack of proper guidance of the toxemic labor.

6. Evidence is presented showing the haste of operative interference before careful study and management of the toxemic mother.

7. The greater vulnerability of the premature and immature toxemic fetus to drugs and interference is discussed.

8. A plea for complete study of the placenta, cord, and envelopes in all stillbirths is presented.

CONCLUSIONS

1. Toxemic patients must be carefully studied and closely watched.

2. There should be careful management of the toxemic labor with special attention to noninterference unless the mother has first been treated; and the use of analgesic and anesthetics should be limited to the very minimum.

3. Inadvisability of cesarean section before the twenty-eighth week unless all other methods fail should be considered.

4. Labor should be induced as soon as the toxemic mother with alarming symptoms (not simply hypertension) does not respond to treatment.

5. Unusually strict and constant supervision of the fetus after delivery should be followed.

REFERENCES

(1) *Dunham, et al.:* Am. J. Pub. Health **28**: 491, 1938. (2) *Schreiber, Frederick:* J. A. M. A. **3**: 1263, 1938.

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DISCUSSION

DR. THADDEUS L. MONTGOMERY.—I am not so optimistic as Dr. Dienna in expecting an early reduction in the fetal mortality from toxemia of pregnancy. I am willing to acknowledge, however, that many of these cases are mismanaged and that more could have been done to further the interest of both mother and child. The handling of such cases and the bringing about of a better result in the mother and child require a high degree of obstetric judgment and oftentimes depend upon the combined opinion of the medical clinician, the ophthalmologist, and the obstetrician, all of whom can make their contribution to diagnosis.

As regards the role played by the placenta and particularly the frequency with which certain necrotic lesions or infarcts are noted in the presence of toxemia of pregnancy, I believe, for many reasons, that the hemorrhagic and necrotic areas which are observed in the placenta of nephritic and toxemic patients are a result of the disease and not the cause of it.

DR. DIENNA (closing).—I do not believe very much can be gleaned from a complete post-mortem examination of an extremely macerated fetus. However, in the case of a nonmacerated toxic fetus, we might learn a great deal from a complete post-mortem examination.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 14, 1941

The following papers were presented:

Two Unusual Cases of Chorioepithelioma. Dr. I. C. Rubin. (For original article, see page 1063.)

Chorioncarcinoma With Clinical, Hormonal and Pathological Findings. Drs. William P. Healy and John A. Kelly. (By invitation.) (To appear in a later issue.)

MEETING OF FEBRUARY 11, 1941

The following papers were presented:

Models, Manikins, and Museums for Obstetrics and Gynecology. Dr. Robert L. Dickinson. (For original article, see page 1075.)

A Comparison of the Classical and Lower Segment Cesarean Section. Dr. George H. Ryder. (For original article, see page 1029.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF DECEMBER 5, 1940

The following papers were presented:

The Salvage of Fetuses in Gravidic Toxemias. Dr. Nicholas P. A. Dienna. (For original article, see page 1079.)

Ovarian Transplantation. (Moving Picture.) Drs. Michael J. Bennett and Newlin F. Paxson.

MEETING OF JANUARY 2, 1941

The following papers were presented:

Spontaneous Painless Parturition in Pregnancy Associated With Transverse Myelitis. Dr. J. Stanley Cohen (by invitation).

Hydatidiform Mole Followed by Chorionepithelioma. Dr. Edward F. McLaughlin.

The Contractile Response of the Pregnant Human Uterus to Posterior Pituitary Extract. Dr. Douglas P. Murphy. (To appear in a later issue.)

Ovarian Hemorrhage. Drs. Mario A. Castallo and Louis Feo.

MEETING OF FEBRUARY 6, 1941

The following paper was presented:

Tumors of the Reproductive System in the Rabbit With Especial Reference to Etiological Relationships and to the Development of Autonomy. Dr. Harry S. N. Greene (by invitation).

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 3, 1941

The following papers were presented:

Supravesical Extraperitoneal Cesarean Section (Waters' Operation). Drs. J. R. Eisaman and B. R. Austin (by invitation). (For original article, see page 1060.)

Purpura Hemorrhagica Complicating Pregnancy. Dr. David O'Laughlin.

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 7, 1941

The following papers were presented:

The Immediate Treatment of Obstetric Hemorrhage and Shock. Dr. Charles A. Gordon. (For original article, see page 1056.)

Studies in Pelvic Iontophoresis of a Choline Compound. Drs. Charles A. Gordon and Alexander H. Rosenthal. (For original article, see page 1043.)

A Method for Preventing or Diminishing Peritonitis From Leakage After Intestinal Resection or Perforation. Dr. Harry Koster.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Basden, Margaret: A Maternity Hospital at the Home Front, Brit. M. J. 2: 453, 1940.

The author describes the effect of war on the routine of a Maternity Hospital at the home front. She discusses the facilities afforded the patients for their protection during air raids, the routine by which these facilities are taken advantage of, the modifications required in the treatment of post-partum and postoperative cases, and the apparent and undetermined results of such modifications in treatment.

Post-partum patients are allowed up a few minutes the day the baby is born and patients having abdominal operations on the fifth postoperative day. Subsequent activity is increased daily.

The favorable results noted include the creation of a carefree and happy atmosphere among the patients, a decrease in morbidity, better uterine involution, considerably less venous thrombosis, and stronger and healthier patients on discharge. The author warns that the early adoption of the erect position may increase the tendency to prolapse and too short a stay in bed after operation or confinement may lead to neurasthenia.

FRED L. ADAIR AND W. H. PHILLIPS.

Thomas, Rufus C.: 3,144 Consecutive Deliveries Without a Maternal Death Due to Pregnancy, Brit. M. J. 1: 562, 1940.

Between Jan. 3, 1938, and June 4, 1939, the Corydon Obstetric Service has conducted 3,144 consecutive deliveries without a maternal death attributable to pregnancy. One mother died of pneumococcal pneumonia on the day of delivery which began seven days before. These cases are drawn from all possible sources.

Complete antenatal, natal, and postnatal care is available to the patients and the services of the Borough obstetrician are available to all medical practitioners in the area.

All prenatal patients with an elevated blood pressure, with or without albuminuria, were hospitalized for observation and study. If at the thirty-second-week examination the patient was found to have a breech presentation, external version was attempted. If unsuccessful, the patient was hospitalized, placed in a Trendelenburg position for one to two hours and another effort made. About 75 per cent were successfully converted.

The lower segment operation was done in 49 per cent of 74 cesarean sections, and 59 of these were done under spinal anesthesia.

The stillbirth rate was 28.9 per 1,000 total births, and infant death rate was 13.9 per 1,000 livebirths for the series.

FRED L. ADAIR AND JOHN R. KIGHT.

Kosakae, J., and Okai, K.: The Onset of Labor Pains by Follicular Hormone Is Induced Through the Posterior Lobe of the Pituitary Body, Jap. J. Obst. & Gynec. 23: 172, 1940.

It was previously shown that follicular hormone may successfully be used to stimulate contractions of the uterus. The authors induced labor by means of placental substance. They believe the mechanism of the production of labor pains

is the acceleration of the secretion of oxytocin, because follicular hormone does not act directly upon the uterus. The authors proved that there was an increase in the oxytocin content of the cerebrospinal fluid in animals after the injection of placental substances. Contractions of the uterus were obtained only after a certain concentration of oxytocin was observed in the cerebrospinal fluid.

J. P. GREENHILL.

Spiller, V.: An Inquiry Into the Hour of Birth, Brit. M. J. 1: 435, 1940.

Of 2,225 patients delivered per vaginam during the years 1934 to 1937 at the Royal Free Hospital, 5.25 per cent more were delivered at night, between 8 P.M. and 8 A.M. than during the day.

FRED L. ADAIR AND JOHN R. KIGHT.

Olivella, J. R.: Hour and Month of Births, Rev. cubana de obst. y ginec. 2: 45, 1940.

Olivella studied the records of more than 22,000 strictly spontaneous births. In cases of multiple births the time of expulsion of the first infant only was noted. Of the above number, 10,590 infants were born between 6 A.M. and 6 P.M.; 11,438 between 6 P.M. and 6 A.M. No great consistency was shown from year to year in the hour of most or least births, but over a five-year period 1,039 infants were born at 1 A.M. and 2 A.M. each, and the hour of least births was 5 P.M., with 777. The author discusses the possible effects of solar influences in initiating labor during the day.

R. J. WEISSMAN.

Paton, D. M.: Studies in Obstetric Analgesia, South. M. J. 33: 626, 1940.

This study was based upon the use of several analgesic agents in two series of patients totaling 958 cases. Of these, 610 received some type of analgesia. The primary aim in the management of these labors was to secure first stage analgesia with amnesia. Medication was given as early in labor as it was safe to do without the risk of checking its progress. A variable degree of restlessness occurred with all the analgesics. It was either absent or only slight in 63 per cent of the patients who were given sodium amyl-beta-bromallyl barbiturate (sigmodal). The complementary use of small doses (gr. 1/6) of "pantopon" with pentobarbital and hyoscine combinations appreciably decreased this undesirable side effect. This drug was omitted when the progress of labor was very rapid and delivery seemed imminent. Effective amnesia was obtained in 80 to 85 per cent of the patients to whom pentobarbital-hyoscine-pantopon and pentobarbital-hyoscine were given; in 65 per cent of the morphine-hyoscine group, and in 64 per cent of those patients in whom sodium amyl-beta-bromallyl barbiturate (sigmodal) was used. Rectal ether is stressed as a valuable analgesic agent for use late in the first stage of labor, or even in the second stage when it might be unsafe to employ other drugs. There was no increased incidence of operative delivery.

Two maternal deaths occurred, neither of which was attributed to the use of analgesic drugs. One very toxic patient died of shock resulting from premature placental separation; she had received 6 grains of sodium iso-amyl-ethyl barbiturate (sodium amytal). The second patient had a retained placenta and death from septicemia occurred two weeks post partum. Early in labor "sigmodal" was given and twelve hours later, pentobarbital and hyoscine.

A total of 15 fetal deaths occurred. Of the two in the first series, one infant was born of an eclamptic mother. Both eclamptic patients received "average effective morphine-hyoscine narcosis." In the second series, there was sufficient cause for the deaths, exclusive of the use of any of the drugs. One of the conclusions of the author is that, "the danger to the baby is negligible in the hands of one trained in the use of analgesics."

ARNOLD GOLDBERGER.

Sharkey, John A.: Should Solution of Posterior Pituitary Be Used in the First and Second Stages of Labor? J. A. M. A. 115: 1315, 1940.

The author emphasizes the fact that solution of posterior pituitary should not be used in normal labor, and again points out the dangers to child and mother, chief of which are intracranial hemorrhage and injury to the musculature of the uterus resulting from tetanic contractions. In cases of uterine inertia the solution of posterior pituitary should be limited to certain cases of true primary inertia and he enumerates several conditions in which it should not be used. Posterior pituitary is certainly not indicated in secondary inertia. The author feels that its use is contraindicated in toxemia of pregnancy, placenta previa, and heart disease, but in skilled hands it can occasionally be advantageously employed in abruptio placentae.

WILLIAM BERMAN.

Kühnel, P.: Further Experience With Scalp Forceps Traction in the Treatment of Uterine Atony, Acta. obst. et gynec. Scandinav. 20: 139, 1940.

The author reports 11 additional cases of protracted labor with secondary atony treated by means of scalp forceps traction. The good results obtained lead him to recommend strongly the use of this method in suitable cases of uterine atony.

J. P. GREENHILL.

Dawson, J. Bernhard: The Occipito-Posterior Position, Brit. M. J. 1: 612, 1940.

A review of 3,700 deliveries revealed 415 cases of occipito-posterior positions, not including those better designated as occipito-lateral or transverse. Of these, 30 per cent delivered face to pubes naturally or with forceps, 50 per cent rotated and delivered naturally or with forceps, and 20 per cent required manual or forceps rotation.

That the size of the infant is not a factor in the persistence of occipito-posterior position was shown by the small difference in infant weights in the above 3 groups. Parity apparently played little part in the etiology of posterior positions, and a predominance of multiparas in the first and second groups does not support the contention that laxity of pelvic tissues may adversely influence anterior rotation. An equal number of primiparas and multiparas required rotation, suggesting a common factor, such as the pelvic type, but this was disproved by a lack of repeated occipito-posterior positions in multiparas.

Infant mortality of the posterior positions compared favorably with that of the entire group, being slightly better for infants that rotated spontaneously.

Average duration of labor was increased in primiparas, but showed little difference in multiparas.

The author's treatment consists of noninterference until the mother's or baby's condition necessitates delivery, or careful examination reveals a failure in the progress of labor. His method of manual rotation is described.

FRED L. ADAIR AND JOHN R. KIGHT.

Guerriero, W. F., Arnell, R. E., and Irwin, J. B.: Pelvicephalography: An Analysis of 503 Selected Cases, South. M. J. 33: 840, 1940.

In order to evaluate the accuracy of the Ball method of pelvicephalography, a clinical and radiologic study was made. It was based upon 503 cases of patients with prolonged labors, evident or suspected fetopelvic disproportion, abnormalities of the bony pelvis, and a number of normal patients selected from a series of over 6,000 deliveries. Other causes of dystocia were eliminated. There were 191 white and 312 colored patients; 362 of the presentations were vertex and 38 were breech.

Roentgen pelvimetry eliminates the ever present, variable factor of personal equation and assures accuracy in the determination of all the pelvic diameters. In addition to pelvic measurements, such other information of clinical value may be ascertained, as details of pelvic architecture, cephalopelvic proportions, the pos-

sible occurrence of intrauterine fetal death, malformations and multiple gestation. This method of pelvimetry requires an anteroposterior and a lateral view of the pelvis. The former reveals the contour of the inlet, the basis for the Thoms classification of pelvic type, which was employed in this analysis, as well as the outline of the ischial spines. The prominence of these spines as a factor in dystocia seems to depend upon the adequacy of the transverse diameter of the midplane, and the adequacy of the posterior half of the midpelvis (''compensation of the posterior pelvis''). When these factors are ample, prominence of the spines per se is not likely to cause dystocia. From the lateral view may be obtained information concerning the lumbar spine, the contour and position of the sacrum, the sacrococcygeal articulation and the hip joint. The most frequent pelvic type was the brachypellic, with an incidence of 48.1 per cent; the mesapellic type was next and occurred in 32.9 per cent. On a racial basis these two types predominate. In the colored patients, these appeared in the same order as for the entire series; among the white patients the order was reversed.

The Ball method of pelvicephalography is based upon volumetric comparisons of the fetal head at the pelvic inlet and at the midplane. By Ball's mechanical calculator, a correction is made for magnification, and then the fetal head circumference and pelvic diameters are determined. These data make possible a calculation of volume capacity of the pelvis and of the fetal head, from which it is possible to make cephalopelvic volume comparisons. Dystocia at the inlet is predicted if the volume of the head exceeds the volume capacity of the inlet by more than 150 milliliters; and miplane dystocia when the fetal head volume exceeds the volume capacity of the midplane by more than 250 milliliters. The authors adopted their own standard of 200 milliliters for the criterion of inlet dystocia. They stress the fact that dystocia often results from a combination of borderline inlet volume relations with a midplane, and emphasize the importance of a consideration of the posterior sagittal dimension in midplane pelvicephalometry. The value of this procedure was decreased in breech presentations, where discrepancies between the x-ray findings and the clinical course occurred.

Roentgen study of the pelvis and cephalopelvic relations by the Ball method provides data which may be of prognostic significance. It should be considered as a laboratory aid, and the results interpreted in the light of clinical judgment and experience.

ARNOLD GOLDBERGER.

Frawley, M. D'Arcy: The Treatment of Disproportions, Canad. M. A. J. **44:** 38, 1941.

The author reports the occurrence of 53 instances of disproportion in 1,000 consecutive deliveries. Its presence was anticipated in two-thirds of the cases. Elective cesarean section was performed in 4 instances. The remaining 49 were subjected to a test of labor. Of them 9 delivered spontaneously, 33 following forceps (1 high forceps), 2 were delivered by version and extractions, and 4 were finally delivered by low segment cesarean section. Craniotomy was performed on one dead infant. There were 2 maternal deaths, both due to infection and 3 infants' deaths due to asphyxia.

CARL P. HUBER.

Long, J. P., Jr., and Stabnick, J. S.: Craniotomy, South. M. J. **33:** 1073, 1940.

There is evidence that craniotomy was performed in antiquity, and that in 3000 B.C. the operation was done in certain difficult labors by priests. The instruments and methods devised by Paré, Levret, Smellie, and Baudelocque are still largely used today with some slight modifications.

The principal indications for the procedure are: (1) where a positive diagnosis of hydrocephalus or other monster formation has been made; (2) in breech presentations when the infant is dead and slight cephalopelvic disproportion exists, or when the head is impacted and the chances of obtaining a live baby are very slight; (3) whenever the baby is dead and cannot be easily delivered by forceps or version; (4) in certain instances where the mother is in a critical condition and a rapid delivery

with the least amount of shock is indicated. Three contraindications to the performance of craniotomy are also indications for abdominal delivery: (1) a true conjugate of less than 5.5 cm.; (2) tumor blocking the pelvis; (3) a fibrous or carcinomatous cervix. A patient who has had one craniotomy should subsequently be delivered in some place where better obstetric facilities are available.

In a ten-year period, during which there were 12,292 deliveries, 29 craniotomies were performed, an incidence of 0.235 per cent. Of these, 12 of the patients had received prenatal supervision in the hospital clinic, and 17 patients were referred from elsewhere. The specific indications for the craniotomies in the series numbered ten. Twenty-four of the infants were dead when the operation was performed; 4 babies were hydrocephalic. The duration of the longest labor was approximately 98 hours. In the majority of instances there was a history of membranes having been ruptured for many hours; the longest periods were 178 hours and 144 hours.

There were 7 maternal deaths, a mortality rate of 24.1 per cent. Six of the deaths occurred in nonclinic patients, and in 5 of them there were vaginal examinations with attempts at delivery in the home. The patients were in poor or critical condition when the operation was performed, and, with the single exception of a patient whose pregnancy was interrupted at five months for medical indications, they had been in labor from 40 to 74 hours. The one clinic patient had a hydrocephalic baby; she was examined vaginally in the hospital and had a bag induction of labor. There was no autopsy and death was ascribed to embolism or surgical shock.

ARNOLD GOLDBERGER.

Item

Postgraduate Course

The Illinois State Department of Public Health and the Children's Bureau, U. S. Department of Labor are sponsoring ten four weeks' courses in obstetrics at the Chicago Lying-in Hospital during the fiscal year 1941-1942. Only a limited number of physicians will be accepted for each course. The only cost to the individual is for room and board and $25.00 ($10.00 of which is refunded at the completion of the course). Applications and inquiries should be addressed to: Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

Books Received

HOLT'S DISEASES OF INFANCY AND CHILDHOOD. By the late L. Emmett Holt and John Howland. Revised by L. Emmett Holt, Jr., M.D., Associate Professor of Pediatrics, Johns Hopkins University, etc., and Rustin McIntosh, M.D., Carpentier Professor of Pediatrics, Columbia University, New York, etc. Eleventh edition, 262 figures, 1421 pages. D. Appleton-Century Company, New York, 1940.

THE MERCK MANUAL. Therapeutics and Materia Medica. Seventh edition, 1436 pages. Merck & Co., Inc., Rahway, N. J., 1940.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by Philip Bard, Professor of Physiology, Johns Hopkins University School of Medicine. Ninth edition, 387 figures, 1256 pages. The C. V. Mosby Co., St. Louis, 1941.

MODERN DRUG ENCYCLOPEDIA. Therapeutic Guide. By Jacob Gutman, M.D., Phar.D., F.A.C.P., Director, Brooklyn Diagnostic Institute, etc. Second edition, 1644 pages. Published by New Modern Drugs, New York City, 1941.

A FAMILY DOCTOR'S NOTEBOOK. By I. J. Wolf, M.D., Professor of Medicine, Emerit. University of Kansas School of Medicine. Fortuny's, New York, N. Y., 1941.

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